RESEARCH ARTICLE

A Common Profile of Disordered Angiogenic Factor Production and the Exacerbation of Inflammation in Early Preeclampsia, Late Preeclampsia, and Intrauterine Growth Restriction

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Abstract

Preeclampsia and intrauterine growth restriction are two separate disease entities that, according to numerous reports, share the same pathogenesis. In both, angiogenesis disorders and generalized inflammation are the dominant symptoms. In this study, we hypothesized that both diseases demonstrate the same profile in early preeclampsia, late preeclampsia, and intrauterine growth restriction patients, with the only difference being the degree of exacerbation of lesions. One hundred sixty-seven patients were enrolled in the study and divided into four groups: early preeclampsia, late preeclampsia, and intrauterine growth restriction groups, and one control group. Concentrations of the angiogenesis and inflammatory markers soluble fms-like tyrosine kinase receptor 1, placental growth factor, high-sensitivity C-reactive protein, and interleukin-6 were determined, and the behavior of these markers and correlations among them were studied. Higher concentrations of soluble fms-like tyrosine kinase receptor 1, high-sensitivity C-reactive protein, and interleukin-6 and a lower concentration of placental growth factor were observed in the study groups compared with the control group. No differences in concentrations of the studied markers were found among the study groups but significant correlations were observed. The higher values for the angiogenesis and inflammatory markers both in preeclampsia patients and patients with intrauterine growth restriction of placental origin compared with the control group suggest the existence of the same underlying disorders in the development of these pathologies. The observed mutual correlations for disordered angiogenesis and inflammatory markers are suggestive of a mutual relationship between these processes in the development of pathologies evolving secondary to placental ischemia. The same lesion profile was observed for both preeclampsia and 'placental' intrauterine...
growth restriction patients, which could be used in developing common diagnostic criteria for pregnant patients.

Introduction

Preeclampsia and intrauterine growth restriction (IUGR) are the main causes of perinatal morbidity and mortality. These diseases affect 6–10% of pregnant women in North America. Impaired trophoblast invasion, and therefore perfusion disorder in the uteroplacental compartment, is seen as the pathogenesis of these conditions. It appears that early preeclampsia, late preeclampsia, and some cases of IUGR share the same placental pathology but show different exacerbations and demonstrate different clinical pictures in the mother and fetus [1]. It is suggested that this group should perhaps be given one name, ‘ischemic placental syndrome’, and treated as a single pathology that presents different clinical pictures.

Studies published to date indicate that a disordered blood supply to the placenta affects angiogenic, anti-angiogenic, and inflammatory factors synthesized by the placenta, and it is these factors that are responsible for the symptoms observed in the mother.

Currently, there are relatively specific markers that allow for assessment of the above processes. Angiogenesis disorder markers include soluble fms-like tyrosine kinase receptor 1 (sFlt-1) and placental growth factor (PIGF), while inflammatory markers include the already quite widely available high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6.

This study examined whether the pathologies related to impaired trophoblast invasion (early preeclampsia before 34 weeks of gestation, late preeclampsia after 34 weeks of gestation, and IUGR) show similar disorders, which may indicate that they share the same pathogenesis. The aim was to assess whether disordered angiogenesis markers sFlt-1, PIGF, and the sFlt-1/PIGF ratio and inflammatory markers hsCRP and IL-6 differed between the study group and the control group, and among study subgroups (early and late preeclampsia and IUGR). Additionally, we sought to determine whether the disordered angiogenesis markers sFlt-1, PIGF, and PIGF as well as the sFlt-1/PIGF ratio correlate with the inflammatory markers hsCRP and IL-6 in early or late preeclampsia patients and in IUGR patients.

Materials and Methods

The study group was 167 pregnant patients hospitalized between 2011 and 2015 at the Clinical Department of Obstetrics and Gynecology, Pomeranian Medical University, Szczecin, Poland. Patients: 42 patients diagnosed with early preeclampsia before 34 weeks of gestation (early); 41 patients diagnosed with late preeclampsia after 34 weeks of gestation (late); 41 patients suffering from IUGR; a control group of 43 patients with physiologically normal pregnancies (control). Each of the 4 groups of specific qualification criteria was subsequently expanded by further qualifying patients until each group reached the planned number of more than 40 patients.

Preeclampsia was diagnosed in patients with high blood pressure (24-h respiratory rate records) and new-onset proteinuria (>0.3 g/24-h in 24-h urine collection). In the absence of proteinuria, preeclampsia was diagnosed as hypertension in association with thrombocytopenia (platelet count <100 000/μL), impaired liver function (raised blood levels of liver aminotransferases to twice the normal concentration), new development of renal insufficiency (elevated serum creatinine >1.1 mg/dL), pulmonary edema, or new-onset cerebral or visual disturbances. IUGR was diagnosed as estimated fetal weight <10th percentile together with
pulsatility index in the umbilical artery >95th percentile or cerebroplacental index <5th percentile. Patients diagnosed with a simultaneous IUGR were excluded. In the IUGR group, no presence of higher arterial blood pressure and/or proteinuria was observed. Cases of IUGR caused by a genetic factor, infection (diagnostic amniocentesis was performed on some patients, while others were analyzed after delivery), or maternal factors were excluded from the IUGR group.

Inclusion criteria for the study were: (a) early preeclampsia, patients admitted to the Clinical Department between 24 and 33 weeks for a singleton pregnancy with symptoms of preeclampsia, without co-morbidities; (b) late preeclampsia, patients admitted to the Clinical Department between 34 and 40 weeks for a singleton pregnancy with symptoms of preeclampsia, without co-morbidities; (c) IUGR, patients between 24 and 40 weeks of gestation with symptoms of IUGR but no symptoms of preeclampsia, after fetal and maternal causes were ruled out. Some patients were only included upon delivery, after fetal genetic causes and fetal infection were ruled out; and (d) control group, patients between 24 and 40 weeks of gestation without any accompanying pathology or chronic disease, hospitalized at our Clinical Department of Obstetrics and Gynecology.

Biochemical determinations were made using standardized kits that make use of the ELISA immunofluorescence technique. In each of the studied women, sFlt-1, PlGF, the sFlt-1/PlGF ratio, hsCRP, and IL-6 were determined. Blood for assessment of the studied parameters was drawn with the patient’s informed consent, and was centrifuged within 30 min of the sample being taken and stored at −80°C until analysis. Blood for routine biochemistry tests was sampled into standard test tubes and transported to the Central Hospital’s laboratory immediately. The results were subjected to statistical analysis using StatSoft software (Poland).

Statistical analysis
Assessment of the normal distribution of continuous variables (Kolmogorov–Smirnov), which was the case for most variables, showed deviation from normal (log normal) schedule parameters. The routine biochemistry tests and the parameters characterizing the group (Table 1) were shown using group size, the median, and the minimum and maximum values. For comparison of the aforementioned parameters between the study group and the control group, a Mann-Whitney U-test was used. The study parameters were characterized by sample size, arithmetic mean, and standard deviation. Distributions of the aforementioned parameters were normalized by being converted into logarithmic continuous variables. To evaluate differences between studied parameters, Student’s t-tests were used for unpaired variables (Table 2) and analysis of variance (ANOVA) and multivariate analysis of variance were used for multivariable systems followed by multiple comparison post-hoc Tukey’s tests. The assumptions required for ANOVA (normality distribution and homoscedasticity) were not violated in any way that could have impaired the credibility of the F statistic. Strengths of correlations between parameters were measured using Pearson’s correlation coefficient (variables with normal distribution) or Spearman’s rank correlation coefficient (variables deviating from normal distribution).

Ethical considerations
The study was performed with the approval of the Bioethics Committee at Pomeranian Medical University (No. n.KB-0012/122/12), and was conducted in accordance with the principles expressed in the Declaration of Helsinki. All participants provided written informed consent to participate in the study.
### Table 1. Characteristics and a statistical analysis of routine diagnostics of the study groups (Mann-Whitney U-test).

| Parameter               | Control (n = 43) | Early (n = 42) | Late (n = 41) | IUGR (n = 41) |
|-------------------------|------------------|----------------|---------------|---------------|
| Parity                  |                  |                |               |               |
| 1                       | (1–3)            | 1 (1–5)        | 1 (1–5)       | 1 (1–5)       |
| 2                       |                  |                |               |               |
| 3                       |                  |                |               |               |
| Gravidity               |                  |                |               |               |
| 1                       | (1–6)            | 1 (1–5)        | 1 (1–5)       | 1 (1–5)       |
| 2                       |                  |                |               |               |
| 3                       |                  |                |               |               |
| Age (years)             | 32 (22–44)       | 33 (19–42)     | 31 (17–42)    | 31 (18–41)    |
| Gestation (weeks)       | 31 (26–33)       | 37 (34–40)     | <0.001        | 36 (22–41)    |
| Height (cm)             | 165 (156–176)    | 165 (156–174)  | 165 (68–179)  | 165 (150–181) |
| Weight (kg)             | 75 (64–125)      | 75 (60–129)    | 69 (52–120)   | 70 (53–129)   |
| RR dia (mmHg)           | 110 (70–146)     | <0.001         | 75 (60–130)   | 70 (50–90)    |
| RR sys (mmHg)           | 182 (110–225)    | <0.001         | 133 (90–160)  | <0.01         |
| Proteinuria (g/24-h)    | 2.01 (0.4–16.23) | <0.001         | 0.00 (0.00–0.00) | 0.00 (0.00–0.00) |
| Fetal weight (g)        | 1180 (590–2380)  | <0.001         | 2130 (670–2700) | <0.001        |
| PT (s)                  | 10 (8.80–11.30)  | 10.20 (9.30–13.30) | 10.30 (9.20–11.90) | 10.30 (9.20–11.90) |
| D-dimers (ng/mL)        | 3760 (683–10000) | <0.001         | 1116.70 (301.5–3198) | <0.001        |
| APTT (s)                | 27.2 (21.50–85.60) | <0.01         | 26.75 (19.80–34.60) | <0.01         |
| Fibrinogen (g/L)        | 3.65 (1.70–7.10) | <0.001         | 4.50 (2.60–10) | 4.30 (2.10–5.90) |
| WBC (10³/L)             | 11.87 (7.32–18.07) | <0.001         | 11.16 (6.56–19.77) | 10.67 (6.17–18.87) |
| Ht (%)                  | 0.34 (0.25–0.40) | <0.01          | 0.35 (0.26–0.42) | 0.34 (0.27–0.40) |
| Hb (mmol/L)             | 7.14 (4.80–9.00) | ns             | 7.20 (5.20–8.90) | 7.40 (5.80–8.50) |
| RBC (10¹²/L)            | 3.88 (2.81–4.59) | ns             | 3.95 (3.15–4.80) | 3.92 (3.26–4.57) |
| PLT (10³/L)             | 139 (39–311)     | <0.01          | 203.0 (100–550 ) | 204.0 (107–351) |
| LDH (U/L)               | 365 (216–2595)   | <0.001         | 197.5 (145–366) | 180.0 (100–550) |
| ALT (U/L)               | 40 (6–692)       | <0.001         | 16.0 (6–102)   | 19.5 (7–73)   |
| AST (U/L)               | 37 (11–1074)     | <0.001         | 20.0 (9–50)    | 19.0 (10–37)  |
| UA (μmol/L)             | 6.4 (2.90–10.70) | <0.001         | 6.55 (4.20–12.00) | <0.001        |

P-value statistically significant differences between the study groups and the control group. Early, patient group with early-onset preeclampsia; Late, patient group with late-onset preeclampsia; IUGR, patient group with intrauterine growth restriction; RR dia, respiratory rate diastolic blood pressure; RR sys, respiratory rate systolic blood pressure; PT, prothrombin time; APTT, activated partial thromboplastin time; WBC, white blood cell count; Ht, hematocrit; Hb, hemoglobin; RBC, red blood cell count; PLT, platelet count; LDH, lactate dehydrogenase; ALT, alanine transaminase; AST, aspartate transaminase; UA, uric acid; ns, not significant; 1: gestational age at inclusion; 2: neonatal birth weight after delivery between the 38th and 42nd weeks of pregnancy.

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### Table 2. Analysis of study parameters between the study groups and the control group using the Student’s t-test.

| Parameter      | Control (n = 43) | Early (n = 42) | Late (n = 41) | IUGR (n = 41) |
|----------------|------------------|----------------|---------------|---------------|
| log sFlt-1     | 3.23 ± 0.26      | 3.96 ± 0.27    | p<0.0001      | 3.98 ± 0.30   | p<0.0001      | 3.64 ± 0.38   | p<0.0001      |
| log PlGF       | 2.58 ± 0.32      | 1.31 ± 0.26    | p<0.0001      | 1.77 ± 0.28   | p<0.0001      | 1.93 ± 0.48   | p<0.0001      |
| log sFlt-1/PlGF| 0.64 ± 0.45      | 2.65 ± 0.36    | p<0.0001      | 2.20 ± 0.38   | p<0.0001      | 1.71 ± 0.69   | p<0.0001      |
| log IL-6       | 0.63 ± 0.21      | 0.86 ± 0.23    | p<0.0001      | 0.86 ± 0.33   | p<0.0001      | 0.73 ± 0.30   | ns            |
| log hsCRP      | –0.33 ± 0.43     | 0.76 ± 0.23    | p<0.0001      | 0.97 ± 0.20   | p<0.0001      | 0.79 ± 0.40   | p<0.0001      |

P-value statistically significant differences between the study groups and the control group. SD, standard deviation; Early, patients with early-onset preeclampsia; Late, patients with late-onset preeclampsia; IUGR, patients with intrauterine growth restriction; sFlt-1, fms-like tyrosine kinase receptor 1; PlGF, placenta growth factor; log sFlt-1, log sFlt-1 concentration in plasma; log PlGF, log PlGF concentration in plasma; log sFlt-1/PlGF; log sFlt-1/PlGF ratio; log IL-6, log interleukin 6 concentration in plasma; log hsCRP, log high-sensitivity C-reactive protein concentration in plasma.

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Results

In the early and late preeclampsia groups hypertension, the value of proteinuria, and the activity of lactate dehydrogenase, aspartate transaminase and uric acid were significantly different to those in the control group (p<0.001). No such differences were identified in the IUGR group. Only in the early preeclampsia group were differences found compared to the control group in respect of the activity of alanine transaminase, platelet count, the hematocrit and WBC. In all the three study groups, D-dimers represented significantly higher values, while APTT was significantly shortened compared to the control group (p<0.01) (Mann-Whitney U-test, Table 1).

A statistical significant increase in the concentration of sFlt-1 was observed in the early preeclampsia group, the late preeclampsia group, and the group of patients with IUGR but without preeclampsia compared with the control group (p<0.0001). PlGF was significantly lower in all three study subgroups compared with the control group (p<0.0001). The sFlt-1/PlGF ratio was significantly higher in preeclampsia patients and IUGR patients compared with the control group (p<0.0001). Concentrations of inflammatory markers IL-6 and hsCRP were significantly higher in all study subgroups compared with the control group (Student’s t-test, Table 2).

Correlations were assessed for the entire study population. The correlation between concentrations of sFlt-1 and PlGF showed a statistically significant negative correlation (p<0.0001, r = −0.56). A positive correlation of similar power was observed between sFlt-1 and hsCRP concentrations (p<0.0001, r = 0.47) (Fig 1), and a negative correlation between concentrations.
of PlGF and hsCRP was observed (p<0.0001, r = −0.55). There was a statistically significant positive correlation between the sFlt-1/PlGF ratio and IL-6 (p<0.001, r = 0.33) and a negative correlation between PlGF and IL-6 (p<0.0001, r = −0.36). There was a significant positive correlation between hsCRP and IL-6 (p<0.01, r = 0.28).

To assess differences among study subgroups and between subgroups and the control group, ANOVA was performed, which returned statistically significant results for all factors. Subsequently, we performed Tukey’s test. Values for sFlt-1 (Fig 2), the sFlt-1/PlGF ratio (Fig 3), hsCRP (Fig 4), and IL-6 (Fig 5) in all study subgroups were higher than that of the control group (p<0.05). For PlGF (Fig 6), values for all subgroups were lower than that of the control group (p<0.05).

**Discussion**

Preeclampsia and IUGR are the main causes of perinatal morbidity and mortality. In many cases, IUGR occurs together with preeclampsia. Frequently, IUGR occurs on its own, presenting clinical symptoms in the fetus, but the mechanism behind the development of the disease is
the same as in preeclampsia [1]. In previous studies [2, 3], examined placentae from IUGR patients showed characteristics of abnormal uterine artery remodeling, and contained numerous lesions of the chorionic villi, suggesting reduced uteroplacental circulation. Lesions included syncytiotrophoblast knots, villous fibrosis, a reduced volume of villi, and non-specific inflammatory infiltration (villitis of unknown etiology). The lesions correlated with changes in uterine artery blood flow assessed using Doppler sonography [2–4].

A combination of abnormal uterine artery flow and the histopathological features of abnormal uterine artery remodeling are also typical of preeclampsia. It appears that the two diseases (IUGR and preeclampsia) share the same etiology. Recent studies have reported similarities in etiologies between preeclampsia and IUGR by examining smooth muscle cells from chorionic villi. In both diseases, reduced expression of cystathionine gamma-lyase, responsible for the synthesis of the vasodilator hydrogen sulfide, was shown to exist. The diminished expression of hydrogen sulfide provides increased resistance in placental vessels, which translates into abnormal profiles obtained with uterine artery Doppler sonography [5]. Similarly, villitis of unknown etiology has been identified in both diseases. Inflammatory infiltration mainly comprises

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Fig 3. Analysis of variance for the soluble fms-like tyrosine kinase receptor 1 (sFlt-1) and placental growth factor (PIGF) ratio in the study groups. The difference between the sFlt-1/PIGF ratio in the study groups with a 95% confidence interval was p<0.0001, F = 133.57. Interactions between groups for the sFlt-1/PIGF ratio using Tukey’s test (examining statistically significant differences) were: intrauterine growth restriction (IUGR)/control (p=0.0001); early/control (p=0.0001); late/control (p=0.0001). log sFlt-1/PIGF, log sFlt-1/PIGF ratio; early, early-onset preeclampsia; late, late-onset preeclampsia.

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histiocytes and lymphocytes [6, 7]. It is suggested that perhaps this group should be given a single name, ‘ischemic placental syndrome’, and treated as one pathology that presents different clinical symptoms. A shared pathogenesis of these diseases is also suggested by studies assessing other parameters showing increased in early and late preeclampsia and IUGR [8].

An abnormal placenta produces angiogenic and anti-angiogenic factors in a disordered manner. In diseases related to placental ischemia, reduced production of PlGF (a factor that stimulates angiogenesis) and increased production of its antagonist (sFlt-1) has been reported [9–12]. Apart from the factors affecting angiogenesis, an ischemic placenta also produces immunologic factors (tumor necrosis factor alpha, IL-6, and IL-8) which lead to generalized inflammation [13]. In the current study, we observed elevated concentrations of sFlt-1, hsCRP, and IL-6 in early preeclampsia, late preeclampsia, and IUGR groups compared with the control group. In the study subgroups, the concentration of PlGF was lower than that of the control group. Similar results have been reported previously. For example, Husse reported that preeclampsia and IUGR groups had higher angiogenesis markers than the control group [14].

![Fig 4. Analysis of variance for high-sensitivity C-reactive protein (hsCRP) in the study groups.](image)

The differences between hsCRP concentrations in the study groups with a 95% confidence interval was p<0.0001, F = 134.29. Interactions between groups for hsCRP using Tukey's test (examining statistically significant differences) were: intrauterine growth restriction (IUGR)/control (p<0.0001); early/control (p<0.0001); late/control (p<0.0001). log hsCRP, log hsCRP concentration in plasma; early, early-onset preeclampsia; late, late-onset preeclampsia.

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Alahakoon reported a shared profile for angiogenesis markers in both preeclampsia and IUGR patients [15]; and the results of a study by Schoofs were the same [16].

Placental pathology involves secretion by the placenta of factors that exacerbate inflammation. CRP is an acute-phase protein [17] mainly synthesized and secreted by hepatocytes, but local synthesis and secretion occur in other cells, such as macrophages and smooth muscle cells [18, 19]. IL-6 is the main stimulator of the production of CRP. It is secreted by activated leukocytes and smooth muscle cells in response to infection or injury, but also by an abnormal ischemic placenta [13, 20, 21]. In the current study, we observed elevated concentrations of hsCRP in the preeclampsia and IUGR groups compared with the control group of healthy pregnant woman. Farzadnia et al. reported high hsCRP content in severe preeclampsia groups, in agreement with our results [22]. Saarelainen et al. reported that the hsCRP content was higher in patients suffering from gestational hypertension during pregnancy than in the same patients after pregnancy [23]. Can et al. also reported high hsCRP levels in preeclampsia patients [24].

From a review of the literature, we were unable to find any reports on hsCRP in IUGR patients. Only Cheng et al. used this marker and confirmed its value when forecasting the

**Fig 5. Analysis of variance for interleukin (IL)-6 in the study groups.** The difference between IL-6 concentrations in the study groups with a 95% confidence interval was \( p<0.0001, F = 7.0022 \). Interactions between groups for IL-6 using Tukey’s test (examining statistically significant differences) were: intrauterine growth restriction (IUGR)/control (not significant); early/control (\( p<0.0001 \)); late/control (\( p<0.001 \)). log IL-6, log interleukin 6 concentration in plasma; early, early-onset preeclampsia; late, late-onset preeclampsia.

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occurrence of IUGR already in the first trimester of gestation [25]. In those studies, IL-6 levels were higher in the preeclampsia and IUGR groups compared with the control group. The results align with findings from other studies of preeclampsia patients; for example, Udenze et al. [26] and Rahardjo et al. [27]. The results of a study of IUGR patients by Elfayomy et al. [28] were similar to our own.

In ischemic placental syndrome patients, the exacerbation of inflammation correlates with the scale of production of anti-angiogenic and angiogenic factors, as evidenced by our findings of a positive correlation between the sFlt-1 concentration and the sFlt-1/PIGF ratio on the one hand and hsCRP and IL-6 concentrations on the other, as well as a negative correlation between the PIGF concentration on the one hand and hsCRP and IL-6 concentrations on the other. Additionally, IL-6 is the main driver behind the production of CRP, as suggested by the observed positive correlation between IL-6 and hsCRP. Reamer et al. reported a positive correlation between sFlt-1 and CRP in patients with HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), but found no correlation is women with preeclampsia [29]. Ouyang et al. observed the same relationship in preeclampsia patients.
We were not able to find any reports in the literature on research that examined the markers studied in the current study that included a group of IUGR patients [30]. In the current study, we observed an elevated concentration of the anti-angiogenic factor sFlt-1 and a decreased concentration of the angiogenic factor PlGF in the study group compared with the control group. Similarly, we observed increased levels of inflammatory factors IL-6 and hsCRP in the study group compared with the control group. The study group included three subgroups, these being early preeclampsia, late preeclampsia, and IUGR patients. Tukey’s test (preceded by ANOVA) was used to examine whether the subgroups differed from each other and from the control group. sFlt-1, hsCRP, and IL-6 in each subgroup were higher than that of the control group. We found no differences among the study subgroups. The PlGF level was lower in all subgroups compared with the control group, and there were no differences among subgroups. These findings suggest that the three disease types, which are still believed to be separate conditions, share the same etiology.

Conclusions

The higher values observed for the angiogenesis and inflammatory markers both in preeclampsia patients and patients with IUGR of placental origin compared with the control group suggest the existence of the same underlying disorders in the development of these pathologies. The observed mutual correlations for disordered angiogenesis and inflammatory markers are suggestive of a mutual relationship between these processes in the development of the pathologies evolving secondary to placental ischemia. We found the same lesion profile for both preeclampsia and ‘placental’ IUGR patients, which could be used in developing common diagnostic criteria for pregnant patients.

Supporting Information

S1 File. Source data. Values of study parameters (sFlt-1, PlGF, IL-6, hsCRP) and weeks of pregnancy in the study groups.
(XLSX)

Author Contributions

Conceptualization: SK EK.
Data curation: SK EK.
Formal analysis: SK BD.
Funding acquisition: SK.
Investigation: SK AT MBJ.
Methodology: SK BD.
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Resources: SK.
Software: SK RR.
Supervision: SK EK.
Validation: SK.
Visualization: SK.
Written – original draft: SK EK.
Written – review & editing: SK BD.

References
1. Figueras F, Gratacos E. Stage-based approach to the management of fetal growth restriction. Prenat Diagn. 2014; 34: 655–659. doi: 10.1002/pd.4412 PMID: 24839087
2. Brosens IA, Robertson WB, Dixon HG. The role of spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu. 1972; 1: 177–191.
3. Gerretsen GG, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to preeclampsia and fetal growth retardation. Br J Obstet Gynaecol. 1981; 88: 876–881. PMID: 7272259
4. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placenta-tion in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol. 1986; 93: 1049–1059. PMID: 3790464
5. Cindrova-Davies T, Herrera EA, Niu Y, Kindom J, Giussani DA, Burton GJ. Reduced cystathionine y-lase and increased miR-21 expression are associated with increased vascular resistance in growth-restricted pregnancies: hydrogen sulfide as a placental vasodilator. Am J Pathol. 2013; 182: 1448–1458. doi: 10.1016/j.ajpath.2013.01.001 PMID: 23410520
6. Labarrere C, Althabe O. Chronic villitis of unknown etiology and maternal arterial lesions in preeclampsic pregnancies. Eur J Obstet Gynecol Reprod Biol. 1985; 20: 1–11. PMID: 4029472
7. Pathak S, Lees CC, Hackett G, Jessop F, Sebire NJ. Frequency and clinical significance of placental histological lesions in an unselected population at or near term. Virchows Arch. 2011; 459: 565–572. doi: 10.1007/s00428-011-1157-z PMID: 22038509
8. Timur H, Daglur HK, Kara O, Kirbas A, Inal HA, Turkmens GG, Yılmaz Z, Elmas B, Uygur D. A study of serum Apo A-1 and Apo B-100 levels in women with preeclampsia. Pregnancy Hypertens. 2016; 6 (2):121–5 doi: 10.1016/j.preghy.2016.04.003 PMID: 27155339
9. Crispi F, Domingu ez C, Llurba E, Martin-Gallan P, Cabero L, Gratacos E. Placental angiogenic growth factor and uterine artery Doppler findings for characterization of different subset in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol. 2006; 195: 201–207.
10. Ahmad S, Ahmed A. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. Circ Res. 2004; 95: 884–891. doi: 10.1161/01.RES.0000147365.86159.5S PMID: 15472115
11. Maynard SE, Min JY, Merchand J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in pre-eclampsia. J Clin Invest. 2003; 111: 649–658. doi: 10.1172/JCI17189 PMID: 12618519
12. Wallner W, Sengerberger R, Strick R, Strissel PL, Meurer B, Beckmann MW, et al. Angiogenic growth factor in maternal and fetal serum in pregnancies complicated by intrauterine growth restriction. Clin Sci (Lond). 2007; 112: 51–57.
13. LaMarca BD, Ryan MJ, Gilbert JS, Murphy SR, Granger JP. Inflammatory cytokines in the pathophysiology of hypertension during preeclampsia. Curr Hypertens Rep. 2007; 9(6): 480–485. PMID: 18367011
14. Hussein S, Gottschlich A, Schrey S, Stepan H, Hoffmann J. Predictive value of the sFlt1/PIGF ratio for the diagnosis of preeclampsia in high-risk patients. Z Geburtshilfe Neonatal. 2014 Feb; 218(1): 34–41. doi: 10.1055/s-0034-1368713 PMID: 24595913
15. Alahakoon TI, Zhang W, Trudinger BJ, Lee VW. Discordant clinical presentations of preeclampsia and intrauterine fetal growth restriction with similar pro- and anti-angiogenic profiles. J Matern Fetal Neonatal Med. 2014 Dec; 27(18): 1854–1859. doi: 10.3109/14767058.2014.880882 PMID: 24397483
16. Schoofs K, Grittner U, Engels T, Pape J, Denk B, Henrich W, et al. The importance of repeated measurements of the sFlt1/PIGF ratio for the prediction of preeclampsia and intrauterine growth restriction. J Perinat Med. 2014 Jan; 42(1): 61–68. doi: 10.1515/jpm-2013-0074 PMID: 23929878
17. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem. 2004; 279: 48487–48490. doi: 10.1074/jbc.R400025200 PMID: 15337754
18. Dong Q, Wright JR. Expression of C-reactive protein by alveolar macrophages. J Immunol. 1996; 156: 4815–4820. PMID: 8648129
19. Kobayashi S, Inoue N, Ohashi Y, Terashima M, Matsui K, Mori T, et al. Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein.
20. Guan H, Wang P, Hui R, Edin ML, Zeldin DC, Wang DW. Adeno-associated virus-mediated human C-reactive protein gene delivery causes endothelial dysfunction and hypertension in rats. Clin Chem. 2009; 55: 274–284. doi: 10.1373/clinchem.2008.115857 PMID: 19056836

21. Jialal I, Verma S, Devaraj S. Inhibition of endothelial nitric oxide synthase by C-reactive protein: clinical relevance. Clin Chem. 2009; 55: 206–208. doi: 10.1373/clinchem.2008.119206 PMID: 19095724

22. Farzadnia M, Ayatollahi H, Hasan-Zade M, Rahimi HR. A comparative study of serum level of vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1 (ICAM-1) and high sensitive C—reactive protein (hs-CRP) in normal and pre-eclamptic pregnancies. Iran J Basic Med Sci. 2013 May; 16(5): 689–693. PMID: 23826490

23. Saarelainen H, Kärkkäinen H, Valtosen P, Punnonen K, Lahtinen T, Heiskanen N, et al. Flow-mediated vasodilation is not attenuated in hypertensive pregnancies despite biochemical signs of inflammation. ISRN Obstet Gynecol. 2012; 2012: 709464. doi: 10.5402/2012/709464. Epub 2012 Jan 17. PMID: 22462005

24. Can M, Sancar E, Harma M, Guven B, Mungan G, Acikgoz S. Inflammatory markers in preeclamptic patients. Clin Chem Lab Med. 2011 Sep; 49(9): 1469–1472. doi: 10.1515/CCLM.2011.232 PMID: 21913791

25. Cheng PJ, Huang SY, Su SY, Hsiao CH, Peng HH, Duan T. Prognostic value of cardiovascular disease risk factors measured in the first-trimester on the severity of preeclampsia. Medicine (Baltimore). 2016 Feb; 95(5): e2653.

26. Udenze I, Amadi C, Awolola N, Makwe CC. The role of cytokines as inflammatory mediators in preeclampsia. Pan Afr Med J. 2015; 20: 219. doi: 10.11604/pamj.2015.20.219.5317 PMID: 26113950

27. Rahardjo B, Widjajanto E, Sujiati H, Keman K. Different levels of IL-1α, IL-6, TNF-α, NF-κB and PPAR-γ in monocyte cultures exposed by plasma preeclampsia and normotensive pregnancy. Pregnancy Hypertens. 2014 Jul; 4(3): 187–193. doi: 10.1016/j.preghy.2014.03.001 PMID: 26104604

28. Elfayomy AK, Habib FA, Almasry SM, Safwat MD, Eldomyat MA. Serum levels of adrenomedullin and inflammatory cytokines in women with term idiopathic intrauterine growth restriction. J Obstet Gynaecol. 2013 Feb; 33(2): 135–139. doi: 10.3109/01443615.2012.721821 PMID: 23445133

29. Reimer T, Rohrmann H, Stuber J, Pecks U, Glocker MO, Richter DU, et al. Angiogenic factors and acute-phase proteins in serum samples of preeclampsia and HELLP patients: a matched-pair analysis. J Matern Fetal Neonatal Med. 2013 Feb; 26(3): 263–269. doi: 10.3109/14767058.2012.733747 PMID: 23020582

30. Ouyang YQ, Li SJ, Zhang Q, Xiang WP, Shen HL, Chen HP, et al. Plasma sFlt-1-to-PIGF ratio is correlated with inflammatory but not with oxidative stress in Chinese preeclamptic women. Arch Gynecol Obstet. 2009 Jul; 280(1): 91–97. doi: 10.1007/s00404-008-0874-2 PMID: 19099313