Differential Diagnosis of Preeclampsia

Remember the Soluble Fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio

Koen Verdonk, Willy Visser, Henk Russcher, A. H. Jan Danser, Eric A. P. Steegers, Anton H. van den Meiracker

Preeclampsia is a pregnancy-associated condition, clinically characterized by hypertension, proteinuria, and progressive edema, affecting 3% to 5% of all pregnancies.1 Preeclampsia can occur in previously healthy women and in women with underlying conditions, such as hypertension, lupus nephritis, or the antiphospholipid syndrome (APS).1,2 Conversely, pregnancy can be a trigger to activate underlying diseases. A well-known example is lupus nephritis, which can flare during pregnancy, especially when the disease is still active in the months preceding pregnancy or during conception.3 In the United States there are yearly ≈4500 pregnancies with systemic lupus erythematosus (SLE), and of these pregnancies, 13% to 35% are complicated by preeclampsia and 14% to 65% by a lupus flare.2 The clinical features of a lupus nephritis flare closely mimic those of preeclampsia. Differentiation between these 2 conditions on clinical grounds can therefore be a challenge, particularly because lupus nephritis itself predisposes to preeclampsia.2,3 However, such differentiation is critical to optimal management: a lupus flare requires initiation or intensification of immunosuppressive therapy, whereas delivery of the child and the placenta is the only treatment currently available for severe preeclampsia.

In recent years, an imbalance between proangiogenic and antiangiogenic proteins derived from the placenta has been suggested to play a role in the pathophysiology of preeclampsia, and measurement of these proteins in the maternal circulation is coming of age as a tool to diagnose or to provide prognostic information of this condition.4,5 Compared with normal pregnancies, the serum concentration of the antiangiogenic soluble Fms-like tyrosine kinase 1 (sFlt-1) is markedly increased, whereas that of placental growth factor (PIGF) is decreased in preeclampsia.6,8–10 Because of the reciprocal changes of these markers, the ratio of sFlt-1/PIGF appears to be a superior marker of (early onset) preeclampsia compared with the individual values of these markers.7,11 In the 3 complicated pregnancies of this grand round, we used the sFlt-1/PIGF ratio as a biomarker to differentiate among superimposed preeclampsia, activation of the underlying disease, or the combined occurrence of these 2 conditions. For all 3 of the patients, sFlt-1 and PIGF were measured by precise ELISA on a fully automated Elecsys system (Roche Diagnostics).12

Case 1

A 41-year–old woman gravida 6, para 0, was admitted to our hospital at 21+1 gestational weeks because of progressive edema in the legs and shortness of breath. In the past 4 weeks she had gained 25 kg in weight. The medical history included an autoimmune hepatitis, diagnosed at 15 years of age. The hepatitis evolved in liver cirrhosis, complicated by portal hypertension with splenomegaly, esophageal varices, prophylactically treated with band ligation, and thrombocytopenia because of hypersplenism. This woman also has an APS with deep venous thrombosis in the right leg and spontaneous spleen infarctions with positive tests for lupus anticoagulant and antiphospholipid antibodies. For the APS, lifelong treatment with the vitamin K antagonist acenocoumarol was initiated. Antinuclear antibodies (ANAs) were incidentally positive. The autoimmune hepatitis had responded well to prednisone and azathioprine, and 2 years before admission, immunosuppressive therapy was discontinued. The obstetric history was as impressively complicated as her general medical history. She had had 5 pregnancies resulting in early miscarriages. Other than the APS, no other explanations for the recurrent pregnancy loss, such as parental karyotype or uterine abnormalities, could be diagnosed. The current pregnancy had occurred spontaneously.

Blood pressure (BP) at a gestational age of 4 weeks was 110/60 mm Hg, serum creatinine concentration 64 μmol/L (reference range, 35–62 μmol/L), and platelet count 40×10^9/L (174–391×10^9/L), whereas liver enzymes were within the reference range. At admission she was treated with low molecular weight heparin (LMWH) at a therapeutic dose.

At physical examination we saw a moderately ill woman with severe edema of the lower extremities and vulva and...
slightly elevated central venous pressure. BP was 150/84 mm Hg, pulse rate 83 bpm, and respiration rate 12/min. Oxygen saturation at room temperature was 97%. At cardiac auscultation, a grade 2/6 early systolic ejection murmur was heard. Auscultation of the lungs was unremarkable. Fetal ultrasonography was normal. Laboratory examination revealed elevated values of creatinine (120 μmol/L [reference range 35–71 μmol/L]) and uric acid (0.59 mmol/L [reference range, (0.12–0.34) mmol/L]). Serum concentrations of total protein (52 g/L [reference range, 57–69 g/L]) and albumin (25 g/L [reference range, 26–45 g/L]) were reduced. Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LD) were <1.5 times elevated. Serum concentration of total bilirubin (20 μmol/L [reference range, 0–14 μmol/L]) was elevated, whereas serum haptoglobin (<0.05 g/L [reference range, 0.28–2.01 g/L]) was reduced. The hemoglobin concentration was 6.9 mmol/L (reference range, 6.8–8.7 mmol/L) and the platelet count 38×10⁹/L. ANA titer was 1:80, anti-double-stranded DNA antibody was negative, and anti SS-A antibody was weakly positive. Analysis of urinary sediment showed 3+ for erythrocytes and 1+ for leukocytes. Urinary casts were absent. Proteinuria was 0.5 g per day. Maternal echocardiography showed a mild degree of mitral valve insufficiency and evidence of elevated right ventricular pressure, suggesting pulmonary hypertension. Abdominal ultrasonography excluded the possibility of an inferior caval or renal vein thrombosis, but a portal vein thrombosis was diagnosed. Pulmonary embolism was excluded on a contrast-computed tomography of the lungs, but bilateral pleural effusion was visible. Within the days after admission, edema further increased and BP rose. Because of the portal vein thrombosis, the dose LMWH was increased, guided by the measurement of antifactor Xa levels. During the hospital stay, renal function deteriorated with a rise in serum creatinine to 200 μmol/L and a further increase in proteinuria to 1.2 g/dL. The platelet count decreased to 18×10⁹/L and hemoglobin to 6.0 mmol/L (reference range, 6.8–8.7 mmol/L). Liver enzymes further increased (AST, 156 U/L [reference range, 0–33 U/L] and ALT, 59 U/L [reference range, 0–33 U/L]), LD increased to 331 U/L (reference range, 0–447 U/L) and total bilirubin to 26 μmol/L. Regarding the differential diagnosis, lupus nephritis; superimposed preeclampsia; hemolysis, elevated liver enzymes, low platelets syndrome; catastrophic APS; and hepatorenal syndrome were considered. Because of the possibility of lupus nephritis, intravenous methylprednisolone was initiated. The hypertension was treated with α-methyldopa and nicardipine. Despite this treatment, her clinical condition deteriorated. Five days after admission, the measurements of sFlt-1 of 84.339 pg/mL and of PI GF of 55.3 pg/mL, resulting in a sFlt-1/PI GF ratio of 1525, strongly suggested the diagnosis of superimposed preeclampsia (Table). Based on this high ratio, the deterioration of the maternal clinical condition and the very early gestational age, implying a poor pregnancy outcome, pregnancy was terminated. At gestational age of 22+0 weeks, labor was induced. Eight hours later an infant boy (body weight, 325 g; P<10) with an APGAR score of 0 was vaginally delivered. The placental weight was 130 g (P10–25), with a maturation exceeding the pregnancy duration. A few regions with infarctions (<5%) were present.

Postpartum furosemide, enalapril and later also spironolactone were given to treat the edematous state and elevated BP. Nine days after delivery the patient could be discharged. Twelve weeks after discharge liver enzymes were in the reference range. Serum protein had increased to 68 g/L and albumin to 33 g/L and platelet count was 50×10⁹/L.

Case 2

A 28-year-old woman, gravida 1, para 0, was referred from another hospital to our department at 27+0 gestational weeks because of proteinuria. Eleven years before admission she was diagnosed with SLE with positive ANA and antitibody-stranded DNA antibodies and manifestations of painful joints, Raynaud phenomenon, and proteinuria attributed to a grade IV lupus nephritis. In the past she had been treated with cyclophosphamide, prednisone, and azathioprine. Prednisone was discontinued 2 years before admission, but azathioprine was continued. The SLE was stable for several years with a proteinuria of ≈3 g per day and a normal serum creatinine concentration. At the first antenatal appointment at 7 weeks of gestation, no signs of active disease were present, and azathioprine treatment was discontinued.

At admission a not acutely ill patient was seen with pronounced edema of the lower extremities and labia. The body weight was 84 kg (65 kg before pregnancy), BP 140/90 mm Hg, and heart rate 84 bpm. Physical examination of heart and lungs was normal, and no signs of active SLE were present. The cardiotocogram and fetal ultrasonography were normal. Biochemical analysis showed a uric acid of 0.27 mmol/L and a serum creatinine of 96 μmol/L. Serum values of AST, ALT, LD, and haptoglobin were normal. C-reactive protein was <1 mg/L, the ANA titer was 1:160, and antitibody-stranded DNA antibody and anti SS-A antibodies were negative. The hemoglobin concentration was reduced (5.6 mmol/L), but platelet and leukocyte counts were normal. Examination of the urine showed a proteinuria of 14.5 g per day and a 1+ dipstick for hemoglobin. At admission she was treated with a prophylactic dose of LMWH and furosemide 40 mg, twice daily. Because a lupus flare was suspected, 60 mg daily of prednisone, 50 mg twice daily of azathioprine, and 200 mg daily of hydroxychloroquine were prescribed. Despite extensive immunosuppressive therapy, proteinuria increased to 20 g per day and edema progressed. In the urinary sediment 1+ erythrocytes, as well as hyaline and granular casts, were detectable. Also, BP increased to 150/100 mm Hg and the patient developed headache and nausea. The cardiotocogram remained normal. In the differential diagnosis we considered a lupus flare most likely, but superimposed preeclampsia could not be excluded. To assist in the diagnosis we measured sFlt-1 and PI GF serum concentrations. sFlt-1 was 1070 pg/mL and PI GF 379 pg/mL, resulting in a ratio of 2.8 (Table). Based on these findings we considered the diagnosis of superimposed preeclampsia highly unlikely. For the lupus flare intravenous pulse therapy with methylprednisone was given, after which prednisone (60 mg daily) was restarted. The pulse therapy had a favorable effect on her general well being, but proteinuria did not
decline and serum albumin concentration decreased to 20 g/L. Furosemide was increased to treat the edema but without detectable effect. α-Methyldopa and labetalol were given to treat the hypertension. At 33+1 weeks, labor was induced because of severe, treatment-resistant edema. A healthy baby boy of 1680 g (P10–25) was delivered. The weight of the placenta (180 g) was below the fifth percentile for the pregnancy duration. Infarctions <5% of the placenta volume were present.

After delivery, BP remained high and was treated with enalapril, hydrochlorothiazide, nifedipine, labetalol, and spironolactone. The lupus nephritis was treated with hydrochloroquine and mycophenolate-mofetil, whereas prednisone was tapered off. Four weeks after delivery the proteinuria had decreased to 2.0 g per day and serum albumin concentration increased to 30 g/L. Serum creatinine at that time was 77 μmol/L.

**Case 3**

A 27-year–old woman, gravida 1, para 0, was referred because of edema and proteinuria at 27+6 gestational weeks. Six years before admission she was diagnosed with class IV lupus nephritis complicated by a severe nephrotic syndrome, treated with prednisone and mycophenolate-mofetil. Four years before admission the lupus nephritis was in complete remission. Serum creatinine concentration by that time was 96 μmol/L and proteinuria 1.5 g/d. She continued to use 3 doses daily of 500 mg of mycophenolate-mofetil and 10 mg/d of prednisone. Because of her wish to become pregnant, mycophenolate-mofetil was replaced by 3 doses daily of 50 mg of azathioprine. BP at 7+5 gestational weeks was 120/75 mm Hg and urinary dipstick 2+ for protein. At 27+4 weeks of gestation she developed edema. BP at this time was 136/87 mm Hg, and urinary dipstick revealed 4+ protein. Serum creatinine was 60 μmol/L, uric acid 0.31 mmol/L, and platelet count 141×10^9/L. Serum concentrations of AST, ALT, and LD were within the reference range. The ANA titer was 1:80 and the antidouble-stranded DNA antibody concentration 10 IU/mL (reference range, 0–10 IU). Medication, apart from azathioprine, consisted of calcium carbasalate, 100 mg daily, and LMWH at a therapeutic dose.

At admission to our hospital, her symptoms were slight headache and edema. At physical examination she appeared in good health. The BP was 135/90 mm Hg, and 2+ ankle edema was present. The cardiotocogram was unremarkable.

### Table. Characteristics of the 3 Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>41</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Gravida, Para</td>
<td>6, 0</td>
<td>1, 0</td>
<td>1, 0</td>
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<tr>
<td>GA at admission</td>
<td>21 wk+1 d</td>
<td>27 wk</td>
<td>27 wk+6 d</td>
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<tr>
<td>Medical history</td>
<td>Autoimmune hepatitis, liver cirrhosis, thrombocytopenia, antiphospholipid syndrome</td>
<td>Lupus nephritis, hypothyroidism</td>
<td>Lupus nephritis, pulmonary embolism</td>
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<tr>
<td>Differential diagnosis</td>
<td>Lupus flare, preeclampsia/HELLP</td>
<td>Lupus flare and/or preeclampsia</td>
<td>Lupus flare and/or preeclampsia</td>
</tr>
<tr>
<td>sFlt-1, pg/mL</td>
<td>84 339</td>
<td>1070</td>
<td>14 082</td>
</tr>
<tr>
<td>PLGF, pg/mL</td>
<td>55.3</td>
<td>379</td>
<td>58.7</td>
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<tr>
<td>sFlt-1/PlGF ratio</td>
<td>1525</td>
<td>2.8</td>
<td>240</td>
</tr>
<tr>
<td>ANA titer</td>
<td>1:80</td>
<td>1:160</td>
<td>1:80</td>
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<tr>
<td>Anti-dsDNA (0–10)*, IU/mL</td>
<td>Negative</td>
<td>Negative</td>
<td>10</td>
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<tr>
<td>C3 (0.84–1.68), g/L</td>
<td>0.3</td>
<td>0.8</td>
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<td>C4 (0.16–0.42), g/L</td>
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<td>0.14</td>
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<td>Uric acid (0.12–0.34), mmol/L</td>
<td>0.59</td>
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<td>0.39</td>
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<td>LD (0–447), u/L</td>
<td>331</td>
<td>389</td>
<td>218</td>
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<td>Creatinin (35–62), μmol/L</td>
<td>158</td>
<td>103</td>
<td>104</td>
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<tr>
<td>ALT (0–33), U/L</td>
<td>59</td>
<td>47</td>
<td>6</td>
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<tr>
<td>AST (0–33), U/L</td>
<td>156</td>
<td>48</td>
<td>14</td>
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<tr>
<td>Hemoglobin (6.8–8.7), mmol/L</td>
<td>6.9</td>
<td>5.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Platelets (150–370)×10^9/L</td>
<td>18</td>
<td>121</td>
<td>218</td>
</tr>
<tr>
<td>GA at delivery</td>
<td>22 wk</td>
<td>33 wk+1 d</td>
<td>31 wk+1 d</td>
</tr>
<tr>
<td>Birth weight (percentile), g</td>
<td>325 (&lt;10)†</td>
<td>1680 (10–25)</td>
<td>1350 (20–50)</td>
</tr>
</tbody>
</table>

HELLP indicates hemolysis, elevated liver enzymes, low platelets syndrome; GA, gestational age; LD, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, antinuclear antibodies; dsDNA, double-stranded DNA; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase 1.

*Values between brackets in the parameter column indicate reference range.

†This was a still birth.
Ultrasound examination of the uterus revealed a structurally normal fetus with an estimated weight of 1300 g (P84–90). At laboratory evaluation, serum uric acid was 0.39 mmol/L, serum creatinine 75 μmol/L, total protein 53 g/L, and albumin 30 g/L, whereas complement factor C4 concentration was slightly decreased (Table). The hemoglobin concentration was 7.3 mmol/L and platelet count 144×10^9/L. Urinary analysis showed hyaline, leukocyte, and granular casts; proteinuria was 4.5 g per day. AST, ALT, and LH were normal. In the differential diagnosis, lupus nephritis flare, superimposed preeclampsia, or a combination of both conditions was considered. Because of the stable clinical condition and early gestational age, the decision was to try to prolong the pregnancy duration. At 30+0 weeks of gestation she developed more headache. Body weight progressively increased (5 kg in 4 days) because of fluid retention, and BP further rose and kidney function deteriorated. In this patient, a low sFlt-1/PlGF ratio of 2.8 argued against this diagnosis.

Next to liver cirrhosis, patient 1 had an APS with positive lupus anticoagulant and antiphospholipid antibodies. The presence of either of these factors increases the risk of developing preterm preeclampsia by a factor 10 and is associated with other obstetric complications, including recurrent pregnancy loss.13,14,17,18 This was exemplified by our patient, because her previous 5 pregnancies ended in early miscarriages. In this patient several diagnoses were considered, including lupus nephritis because of the deterioration of renal function for which intravenous methyprednisolone was given. The outcome of the subsequently determined sFlt-1/PlGF ratio of 1525 was consistent with the diagnosis of superimposed preeclampsia, aiding in the decision to terminate the pregnancy.

Patient 2 was known to have lupus nephritis that had been in remission for 4 years while she was still on azathioprine treatment. At 7 weeks of gestation, azathioprine was discontinued by her referring obstetrician. This was an unfortunate decision, because flares of lupus are reported to occur in 30% to 60% of pregnant SLE patients.19–22 At admission to our department triple immunosuppressive therapy was initiated, and immunosuppressive therapy was later intensified, but proteinuria and BP increased, raising the question of the presence of superimposed preeclampsia. The low sFlt-1/PlGF ratio of 2.8 argued against this diagnosis. Despite this low ratio, the progressive edema, attributed to the severe proteinuria and hypoproteinemia, required induction of labor.

Patient 3 was treated with azathioprine during her pregnancy because of a lupus nephritis. Despite this treatment, proteinuria progressively increased to 21 g per day. Furthermore, BP rose and kidney function deteriorated. In this patient, a lupus flare or a lupus flare plus superimposed preeclampsia was considered. The result of sFlt-1/PlGF ratio of 240 favored the latter possibility.

**sFlt-1/PlGF Ratio as a Diagnostic Test**

The sFlt-1/PlGF ratio in our patients was used to assist in the distinction between superimposed preeclampsia from activation of underlying diseases. sFlt-1 is a splice variant of the fms-like tyrosine kinase or vascular endothelial growth factor receptor 1, lacking the transmembrane and cytoplasmic domain of the receptor. sFlt-1 is detectable in serum at low concentrations of superimposed preeclampsia, aiding in the decision to terminate the pregnancy.

**Discussion**

We first briefly elaborate on the various problems that complicated the pregnancies of our patients before further discussing the diagnostic usefulness of the sFlt-1/PlGF ratio in superimposed preeclampsia. Patient 1 had liver cirrhosis because of autoimmune hepatitis and an APS. Pregnancy in liver cirrhosis is rare, and, when it occurs, the risk of hepatic decompensation is high.13,14 In a recent study the overall maternal complication rate in patients with autoimmune hepatitis was ≈40%.15 Women with cirrhosis had the highest risk of complications, including hepatitis flare and liver decompensation, but preeclampsia was not observed.15 We wondered whether the preeclampsia in this patient was complicated by the hemolysis, elevated liver enzymes, low platelets syndrome. Because of the hypersplenism, platelet count was already low before pregnancy and further declined during the course of pregnancy, whereas LD as a sign of hemolysis modestly increased, yet remaining below the proposed cutoff value of 600 U/L.16 Interpretation of the significance of the reduced haptoglobin concentration as a hemolysis parameter in this patient was difficult, because cirrhosis may reduce its synthesis. Serum concentrations of AST and ALT were within the reference range before and after pregnancy and moderately increased (AST 5-fold and ALT 2-fold, upper limit of the reference range) at the time that preeclampsia was diagnosed.

Patient 2 had an APS with positive lupus anticoagulant and antiphospholipid antibodies. The presence of either of these factors increases the risk of developing preterm preeclampsia by a factor 10 and is associated with other obstetric complications, including recurrent pregnancy loss.13,14,17,18 This was exemplified by our patient, because her previous 5 pregnancies ended in early miscarriages. In this patient several diagnoses were considered, including lupus nephritis because of the deterioration of renal function for which intravenous methyprednisolone was given. The outcome of the subsequently determined sFlt-1/PlGF ratio of 1525 was consistent with the diagnosis of superimposed preeclampsia, aiding in the decision to terminate the pregnancy.

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of sFlt-1 is considerably higher and that of PIGF lower in pre-eclampsia, especially in early onset preeclampsia. Because of the reciprocal changes of circulating values of sFlt-1 and PIGF in preeclampsia compared with values in normal pregnancy, the ratio of these 2 markers as a diagnostic test for preeclampsia has been advocated. Meanwhile fast and accurate assays working on existing diagnostic platforms, including a point-of-care assay, have been developed. The diagnostic performance of the sFlt-1/PIGF ratio is better than that of the individual values of sFlt-1 and PIGF. With a cutoff value of 85, the reported sensitivity and specificity of the sFlt-1/PIGF ratio are 89% and 97% (area under the receiver operating characteristic curve, 0.97) for preterm preeclampsia and 74% and 89% (area under the receiver operating characteristic curve, 0.87) for late-onset preeclampsia. In the 2 patients who we considered to have preeclampsia, the sFlt-1/PIGF ratios clearly exceeded the cutoff value of 85. The low sFlt-1/PIGF ratio of 2.5 in the second patient was below the 25th percentile of the ratio observed in healthy pregnancies, thereby making the diagnosis of preeclampsia highly unlikely.

Apart from being a test to diagnose preeclampsia, recent research has shown that the sFlt-1/PIGF ratio is also strongly associated with subsequent maternal and perinatal adverse outcomes. In women presenting at <34 weeks of gestation, the sFlt-1/PIGF ratio performs better than other currently available clinical signs and laboratory tests, like BP, and serum concentrations of creatinine, uric acid, and ALT in the prediction of adverse outcomes. Furthermore, the sFlt-1/PIGF has been found to discriminate well between patients with preexisting hypertension or gestational hypertension and patients with superimposed preeclampsia.

### Factors Influencing the sFlt-1/PIGF Ratio

To be a useful diagnostic test to differentiate activation or new onset of an underlying condition mimicking pre-eclampsia from (preterm) preeclampsia, the sFlt-1/PIGF ratio should not or only to a minimal extent be affected by the underlying condition. Patients 2 and 3 both had a lupus nephritis flare, but notwithstanding that the pregnancy duration was comparable, their sFlt-1/PIGF ratios differed considerably. In patient 2, the sFlt-1/PIGF ratio was between the reported 2.5 to 25th percentile of normal pregnancy, and in patient 3 it was considerably higher than the proposed cutoff value of 85. These findings are reassuring, but obviously more data are required to ascertain that a lupus flare itself has no substantial influence on the sFlt-1/PIGF ratio. Data about the relationship between SLE and proangiogenic and antiangiogenic factors during pregnancy is limited and not uniform. In a retrospective case-control study concerning 52 SLE pregnancies (blood sampled between 22 and 32 weeks of gestation), the serum concentration of sFlt-1 was significantly higher in the SLE pregnancies with (superimposed) preeclampsia (n=18) than in those without preeclampsia (1768 versus 1177 pg/mL), whereas the serum PIGF concentration between the 2 groups did not differ. Further prospective studies with repeated determination of the sFlt-1/PIGF ratio are required to clarify whether SLE during pregnancy, either active or not, has influence on the sFlt-1/PIGF ratio and whether the rise in this ratio, characteristic for early onset preeclampsia, is still fully present.

Of potential concern is a recent finding by Rosenberg et al showing that heparin treatment during pregnancy is associated with increased sFlt-1 levels. This increase was detectable after the 28th week of pregnancy in women who, for various reasons, were treated with prophylactic or therapeutic doses of mostly LMWH but in whom pregnancy course and outcome were uneventful. In women on heparin, the serum sFlt-1 concentration in the third trimester was ≈2 times higher than in women off heparin (4596 versus 2612 pg/mL). The heparin-induced increase in sFlt-1 concentration is attributed to shedding of the extracellular domain of the Flt-1 receptor from the placental tissue, caused by heparin displacing the sFlt1 heparin-binding site from the extracellular matrix. Our first described patient was treated with a therapeutic LMWH dose from the early beginning of gestation because of her APS. Our second and third described patients started with a prophylactic LMWH dose at 7 weeks of gestation. Because no repeated measurements were performed, we cannot exclude the possibility that the elevated sFlt-1 concentrations in patients 1 and 3 were attributable, at least in part, to heparin treatment. Contrary to the study of Rosenberg et al, the elevated sFlt-1 concentration in patient 1 was already present in the second trimester of pregnancy. Moreover, in both patients, the serum sFlt-1 concentrations were considerably higher (84 339 in patient 1 and 14082 in patient 3) than those reported by Rosenberg et al.

The effect of intrauterine growth restriction on circulating sFlt-1 or PIGF levels or their ratio has been reported in several studies. The results of these studies are conflicting, which in part might be related to the used definition of intrauterine growth restriction, the time of blood sampling in relation to gestational age, and whether preeclampsia had been excluded. In a relatively large study, Chaivorapongs et al reported higher sFlt-1 levels in small-for-gestational-age pregnancies compared with control pregnant women, but these levels were still considerably lower than in preeclamptic women. Moreover, in line with other reports, sFlt-1 levels were elevated only in small-for-gestational-age patients with abnormal uterine artery Doppler velocimetry examination.

### New Developments

The angiogenetic markers here discussed have an excellent diagnostic accuracy to distinguish (superimposed) preeclampsia from other pregnancy-related conditions associated with hypertension and proteinuria but are not sensitive enough to serve as an early screening test. Meanwhile, proteomic, metabolomic, and gene expression profiling of maternal plasma, urine, or peripheral blood mononuclear cells have been applied to search for new biomarkers and potential pathogenetic pathways. It should be acknowledged that these techniques are not suited for simple, low-cost routine clinical prediction of preeclampsia but for the identification of new biomarkers.
Since early 2000, an imbalance between antiangiogenic and proangiogenic factors has been recognized as an important pathogenetic mechanism in the development of preeclampsia. At this moment the only remedy for pre-eclampsia is delivery of the child and placenta, and albeit beneficial for the health of the mother, it is associated with neonatal morbidity and mortality and high healthcare expenditure. A promise for the future is that normalization of the neonatal morbidity and mortality and high healthcare expenditure is beneficial for the health of the mother, it is associated with eclampsia is delivery of the child and placenta, and albeit in preterm preeclampsia with the objective to prolong pregnancy and to improve its outcome.

In a clinical pilot, the possibility of extracorporeal removal of sFlt-1 using a negatively charged dextran cellu-
lose column to absorb sFlt-1 in 3 patients with very preterm preeclampsia has been reported. This pilot showed that, with this approach, elevated circulating sFlt-1 levels can be reduced, leading to a reduction in proteinuria and stabilization of BP without negative maternal or fetal effects. Thus, the sFlt-1/PIGF ratio can be applied as a diagnostic tool in the differential diagnosis of preeclampsia and has potential as a biomarker to initiate and monitor new treatment options in preterm preeclampsia with the objective to prolong pregnancy and to improve its outcome.

Disclosures

None.

References


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