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*Case Report*

# Severe Superimposed Preeclampsia with Obesity, Diabetes and a Mild Imbalance of Angiogenic Factors

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**Preeclampsia may be due to an excess of circulating anti-angiogenic growth factors derived from the placenta, but metabolic syndrome-like disorders may also set off a cascade of placental and systemic inflammation and oxidative stress. We present a case of severe superimposed preeclampsia with obesity, diabetes and a mild imbalance of angiogenic factors, in which diet therapy ameliorated the preeclamptic signs while improving the adiponectin level. A 41-year-old pregnant woman with obesity and diabetes was referred to our hospital because of severe proteinuria and hypertension at 22 weeks of gestation. After administration of insulin and hydralazine with diet therapy, her hypertension and proteinuria were ameliorated with a 15-kg weight loss. Her adiponectin level was low and her leptin level was high, but her angiogenic factor levels were within the normal ranges for pregnant women at admission. The diet therapy ameliorated her hypertension and proteinuria while improving her adiponectin level as she achieved weight loss. This case suggests that diet therapy for obese preeclampsia patients with a mild imbalance of anti-and pro-angiogenic factors may play an important role in managing preeclampsia. Measurements of maternal adipocytokines and angiogenic factors may be important to distinguish the main cause of preeclampsia, *i.e.*, poor placentation or maternal constitutional factors, for managing preeclampsia in patients with obesity.**

**Key words:** adipocytokine, angiogenic factor, diet therapy, obesity, preeclampsia

Preeclampsia is characterized by the onset of high blood pressure and proteinuria. It occurs in about 3–5% of all pregnancies and results in substantial maternal and neonatal morbidity and mortality [1, 2]. Although the etiology of preeclampsia is still unclear, recent studies suggest that its major phenotypes, hypertension and proteinuria, may be due to an excess of circulating anti-angiogenic growth factors derived from the placenta [2]. In addition, insulin resistance has been implicated in the pathophysiology of preeclampsia. Types 1 and 2 diabetes, gestational diabetes and polycystic ovarian syndrome are also well known to be risk factors for preeclampsia [3]. Several reports have also demonstrated that a higher body mass index (BMI) increases the risk of preeclampsia, suggesting that obesity is an important risk factor for preeclampsia [4]. Moreover, we previously demonstrated that insulin resistance with adipocyte dysfunction may play a role in the pathophysiology of preeclampsia in obese women [5–7]. These data suggested that predisposing cardiovascular or metabolic risks for endothelial dysfunction such as insulin resis-

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tance and obesity, as part of an exaggerated systemic inflammatory response, might dominate in the origins of maternal preeclampsia [8]. Because we have not experienced superimposed preeclampsia patients with good responsiveness to the diet therapy for long periods, even in cases described in our previous report [5], we present a case of severe superimposed preeclampsia with obesity, diabetes and a mild imbalance of antiangiogenic and proangiogenic factors, in which diet therapy ameliorated the preeclamptic symptoms associated with improved adipocyte function.

## Case Report

A 41-year-old obese woman (prepregnant BMI: 40.0) was referred to our hospital because of severe proteinuria and hypertension at 22 weeks of gestation. Before the referral to our hospital, she received sulfonylurea, and her HbA1c was 5.3%, with mild proteinuria and normal blood pressure. She had been diagnosed with overt diabetes and received insulin therapy during a pregnancy at 35 years of age. During that pregnancy, she had only mild proteinuria without hypertension and delivered a healthy female infant weighing 3,300 g at 39 weeks of gestation. After the previous delivery, she dropped out of follow-up care and received no medication for diabetes, although her weight gain was over 30 kg (75 to 109 kg). Her past history was unremarkable except for diabetes and obesity. Laboratory data at admission showed normal liver and renal function but anemia, severe proteinuria (4 g/day) and hypertension (188/115 mmHg) (Table 1). After the initiation of insulin and hydralazine administration, her hypertension and proteinuria were ameliorated with a 15-kg weight loss with change of her dietary calories (from 1,400 to 2,000 kcal) to avoid ketonuria, and she took no medication for hypertension from 25 weeks of gestation to delivery (Fig. 1). She had moderate non-proliferative diabetic retinopathy, but it was not progressive during this pregnancy. Fetal growth was normal, and she delivered a healthy male infant weighing 3,280 g at 37 weeks of gestation. We did not find any evidence of hypercalcemia or hypoglycemia in the newborn. The placenta showed almost normal villous morphology. Because the patient had moderate to severe proteinuria (1–2 g/day) at 6 months after giving birth, we conclude that severe diabetic nephropathy might have been present before this pregnancy.

We retrospectively examined the patient's circulating adiponectin, leptin, antiangiogenic factors (soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng)) and proangiogenic factor (placental growth factor (PlGF) levels) by specific enzyme-linked immunosorbent assays following the manufacturer's instructions (R&D Systems, Inc., Minneapolis, MN, USA) using serum that had been stored at −80℃ as described in our previous report [5]. All samples were examined in duplicate, and samples for measurement of sFlt-1, sEng and adiponectin were diluted 1/100 prior to the assay. As the patient achieved weight loss, her adiponectin level increased with amelioration of the hypertension and proteinuria, but her leptin level remained unchanged during the preg-

**Table 1** Laboratory data at admission

| | | | | | |
|---|---|---|---|---|---|
| WBC | 8.19 $\times 10^3$/ml | Hb | 9.2 ↓ g/dl | Plt | 377 $\times 10^3$/ml |
| RBC | 2.88 ↓ $\times 10^3$/ml | Ht | 25.1 ↓ % | PT | 10.8 sec |
| APTT | 27.6 sec | AT-III | 82 % | D-dimer | 5.2 ↑ mg/ml |
| Fibrinogen | 832 ↑ mg/dl | FDP | 7.7 ↑ mg/ml | | |
| TP | 5.5 ↓ g/dl | ALP | 170 IU/l | Ca | 8.3 mg/dl |
| Alb | 2.5 ↓ g/dl | LAP | 86 IU/l | Mg | 1.6 mg/dl |
| TTT | 1.5 KU | $\gamma$ GTP | 5 IU/l | BUN | 7.5 mg/dl |
| ZTT | 4.3 KU | CHE | 271 IU/l | Cr | 0.55 mg/dl |
| T-bil | 0.39 mg/dl | LDH | 248 ↑ IU/l | UA | 4.4 mg/dl |
| D-bil | 0.04 mg/dl | Na | 138 mmol/l | T-chol | 261 ↑ mg/dl |
| AST | 13 IU/l | K | 3.7 mmol/l | TG | 278 mg/dl |
| ALT | 6 IU/l | Cl | 107 mmol/l | HDL-chol | 69 mg/dl |
| CRP | 0.95 mg/dl | Hp | 60 mg/dl | | |
| Urinary protein | 4383 ↑ mg/day | 24hCCR | 119.4 ml/min | eGFR | 90.3 ml/min/1.73m$^2$ |
| ANA | <5.0 index | Anti-cardiolipin ab | 0.1 U/ml | Anti-cardilipin $\beta$2 ab | <1.2 U/ml |

nancy (Fig. 1). The adiponectin level at 22 weeks of gestation was lower than the range of obese patients with early-onset preeclampsia but was increased and eventually was higher than the range of obese patients with late-onset preeclampsia, while the leptin level was lower than the range of preeclampsia patients during pregnancy, based on our previous study [5] (Table 2). The concentrations of sFlt-1, PlGF and sEng at admission (22 weeks of gestation) were within the normal pregnancy ranges for the second trimester, based on our previous study [5]. Furthermore, although the sFlt-1 and sEng levels were elevated and the PlGF level was decreased, the sFlt-1 and PlGF levels were within the normal pregnancy ranges for the third trimester and the sEng level was higher than the normal pregnancy range for the third trimester, though it was not within the range of late-onset preeclampsia (Table 3). The measurements of adipocytokines and

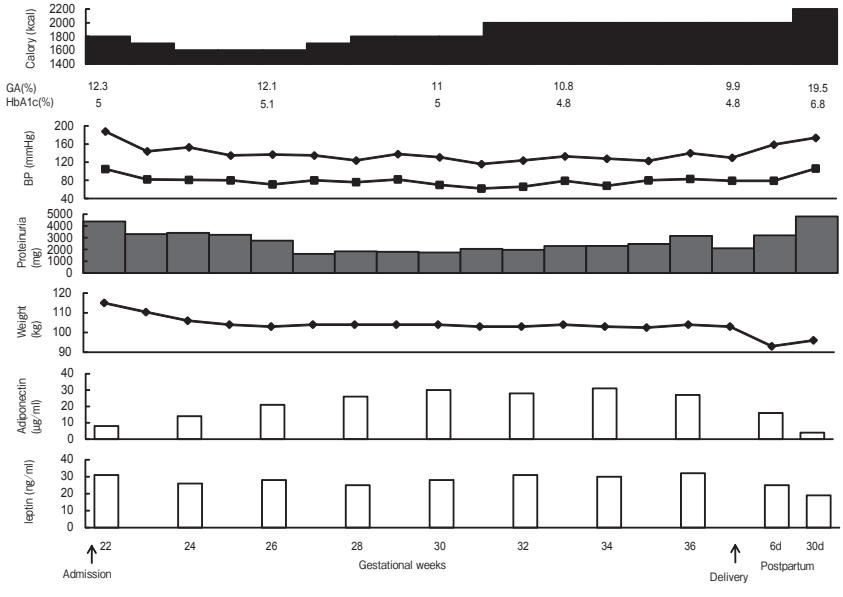


**Fig. 1** Clinical course and maternal concentrations of adipocytokines.

**Table 2** Summary of adipocytokine levels during pregnancy

| | Patient | | Normal pregnancy with obesity | | Preeclampsia Patients with obesity | |
|---|---|---|---|---|---|---|
| | 22w | 36w | early control | late control | early onset | late onset |
| Adiponectin (μg/ml) | 8.1 | 27.4 | 9.0 (6.8–12.1) | 8.8 (6.4–10.5) | 12.4 (8.3–16.8) | 15.8 (12.1–18.3) |
| Leptin (ng/ml) | 31.2 | 32.6 | 29.1 (23.5–32.8) | 23.7 (18.9–27.6) | 56.9 (42.3–70.4) | 42.3 (33.1–51.7) |

[median (interquartile range)]

**Table 3** Summary of angiogenic factor levels during pregnancy

| | Patient | | Normal pregnancy with obesity | | Preeclampsia Patients with obesity | |
|---|---|---|---|---|---|---|
| | 22w | 36w | early control | late control | early onset | late onset |
| sFlt-1 (pg/ml) | 744.2 | 1,733.1 | 490.4 (244.7–833.2) | 1,520.3 (955.7–1,899.2) | 6,270.2 (3,980.4–8,003.5) | 3,324.0 (2,690.0–4,122.2) |
| PlGF | 650.4 | 193.6 | 820.6 (677.4–944.0) | 238.8 (180.5–270.2) | 64.2 (24.3–111.1) | 174.5 (108.8–203.7) |
| sEng (ng/ml) | 10.4 | 20.2 | 6.7 (2.7–11.8) | 10.4 (5.9–12.8) | 90.7 (78.9–108.2) | 42.2 (31.9–54.9) |

[median (interquartile range)]

angiogenic factors were approved by the Institutional Ethical Board of Okayama University Hospital, and the subject provided informed consent for study participation.

## Discussion

Although the cause of preeclampsia remains elusive, the primary origin of the condition is thought to be the placenta. Placenta-derived factors potentiated and may be partly responsible for the maternal syndrome of preeclampsia. The result is a generalized endothelial dysfunction manifested by hypertension, proteinuria and thrombotic microangiopathy [9]. Recent studies have demonstrated that altered release of antiangiogenic and proangiogenic factors, such as sFlt-1, PlGF and sEng, from the placenta may contribute to the pathophysiology of preeclampsia [10, 11]. In the present case, we observed only a mild imbalance of antiangiogenic and proangiogenic factors, and the patient's angiogenic factor levels were within the normal ranges at admission and were slightly elevated or decreased but not within the ranges of late-onset preeclampsia at 36 weeks of gestation. Because she might have had severe diabetic nephropathy and diabetic retinopathy before this pregnancy, the renal and endothelial dysfunction might have contributed to the development of preeclampsia. Moreover, elder maternal age is a risk factor for preeclampsia through age-dependent endothelial dysfunction by maternal constitutional factors [4, 11]. These data suggested that placenta-derived angiogenic factors may not have played an important role and maternal constitutional factors may have been dominant in the pathogenesis of superimposed preeclampsia in this patient.

Adipose tissue expresses various secretory proteins, such as leptin, tumor necrosis factor and adiponectin, that regulate energy expenditure, lipid metabolism and insulin resistance [12]. Abnormal adipocytokine levels are often observed in preeclampsia patients. Placental leptin production is elevated under hypoxic conditions [13], and leptin levels in women with preeclampsia are significantly higher than those in women with normal pregnancies [14–16]. Leptin derived from the placenta may play a role in the pathophysiology of preeclampsia through increased insulin resistance, autonomic activation or direct effects on the endothelium as a placenta-derived factor, as well as an angiogenic factor. Recent reports have also demonstrated that plasma adiponectin concentrations are not elevated in women with normal pregnancies but are paradoxically elevated in women with preeclampsia [17–19]. Furthermore, significant differences in the adiponectin levels have been found between normal and overweight women, but only among those with late-onset preeclampsia [5]. Since hypoadiponectinemia is associated with impaired endothelium-dependent vasodilatation [20, 21] and is an independent risk factor for hypertension [22], adiponectin may maintain endothelial function, and its deficiency may lead to endothelial dysfunction or hypertension. In our case, the hypertension and proteinuria were ameliorated with improved adiponectin levels as the patient's weight decreased, suggesting that diet therapy may play roles in the pathogenesis of preeclampsia with obesity and in the mild imbalance of angiogenic factors. Elevated leptin in the serum is mainly derived from the placenta, whereas adiponectin originates from adipose tissues [13, 23], and in our case we observed that the adiponectin level was increased but the leptin level was not changed under diet therapy. Although the multifactorial pathogenesis of different preeclampsia phenotypes has not been fully elucidated, these findings suggest that measurements of adiponectin and angiogenic factor levels may be important for distinguishing whether the main cause of preeclampsia is poor placentation or maternal constitutional factors, in cases of managing preeclampsia with obesity.

In the present case, we observed abnormal adipocytokine levels but a mild imbalance of antiangiogenic and proangiogenic factor levels, and weight loss under diet therapy improved the adiponectin level, resulting in amelioration of the preeclamptic symptoms, blood pressure and proteinuria. These findings suggest that diet therapy for obese preeclampsia patients with a mild imbalance of antiangiogenic and proangiogenic factors may play an important role in the management of preeclampsia as well as diabetes through improved adipocyte function. Furthermore, measurements of maternal adiponectin and antiangiogenic and proangiogenic factor levels may be important for the management of preeclampsia with obesity.

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