Preeclampsia before 20 weeks of gestation: a case report and review of the literature

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Abstract The occurrence of preeclampsia before 20 weeks of gestation is rare and usually associated with trophoblastic diseases or antiphospholipid syndrome. Here, we report a case of preeclampsia before 20 weeks of gestation in the absence of the aforementioned disorders. A healthy 30-year-old nulliparous woman presented with new onset of hypertension and proteinuria at 18 weeks of gestation. Fetal ultrasound did not reveal any abnormalities. Empirical steroid treatment was initiated based on a tentative diagnosis of underlying renal disease. The clinical course of the disease was progressive despite steroid treatment and the fetus died in utero 8 days after the initiation of treatment. Following delivery, a renal biopsy was performed and provided a diagnosis of preeclampsia. All symptoms resolved postpartum. This report demonstrates that preeclampsia may occur before 20 weeks of gestation and should always be considered in the differential diagnosis of pregnant women with new onset of hypertension with proteinuria. Previous published cases are summarized briefly.

Keywords Preeclampsia · Hypertension · Proteinuria · Endotheliosis · Early onset

Introduction

By definition, preeclampsia occurs after 20 weeks of gestation [1]. Development of hypertension and proteinuria before the 20th week of gestation suggests underlying renal disease rather than preeclampsia [2–4]. Here, we describe a patient presenting with sudden onset of hypertension and proteinuria at 18 weeks of gestation diagnosed with preeclampsia based on renal biopsy findings. We also analyzed and reviewed the limited number of published cases involving the development of preeclampsia before the 20th week of gestation.

Case report

A 30-year-old nulliparous woman at 18 weeks of gestation presented with a 1-week history of worsening leg edema and was admitted to a local hospital for hypertension (blood pressure range: 150–160/100 mmHg) with proteinuria (3+ on a urinary dipstick). All of her previous prenatal follow-up visits were uneventful; her blood pressure was 127/70 mmHg and her urinalysis was normal at her last visit (16 weeks of gestation). Over the next 6 days while on bed rest, her blood pressure remained elevated and 24-h urine protein increased from 0.55 to 2.1 g/day. She was transferred to our hospital for close observation.

Physical examination revealed pitting leg edema, a blood pressure of 149/106 mmHg, and a pulse rate of 88 beats/min. Her height was 160 cm, weight was 87.2 kg, and body mass index prior to pregnancy was 33.6 kg/m².

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Fig. 1 Clinical course of the patient

The patient had no history of hypertension, renal disease, diabetes mellitus, or illicit drug use, and no family history of preeclampsia. Results from laboratory investigations were consistent with nephrotic syndrome. Twenty-four-hour urine protein was 4.0 g/day and serum albumin was 2.8 g/dL. Urinalysis revealed a protein level of 3+ and trace hemoglobin with 1–4 red blood cells and no cellular casts per high-power field. Renal function was normal (creatinine 0.6 mg/dL, estimated glomerular filtration rate ≥ 90 mL/min). Uric acid was 6.9 mg/dL. Complete blood count, and clotting and liver function test results were normal. Connective tissue disease screening including antiphospholipid antibodies were all negative. Thyroid function and the levels of protein C and protein S were normal. Her hemoglobin A1c level was 4.9 %, and a 75-g oral glucose tolerance test showed that her fasting plasma glucose was 69 mg/dL and her 2-h value was 133 mg/dL. An ultrasound scan revealed a single fetus without any anomalies or intrauterine growth restriction. Umbilical artery Doppler showed a normal resistance index of 0.72.

Her clinical course is shown in Fig. 1. Following the initiation of treatment with 750 mg of methyldopa 3 times per day, her blood pressure stabilized at 140–150/90–100 mmHg. However, urinary protein excretion and body weight were increased rapidly in a short period. The onset of hypertension with proteinuria in the nephrotic range before 20 weeks of gestation was considered to support a diagnosis of underlying renal disease rather than preeclampsia. Based on concerns regarding an increased risk for bleeding due to hypertension, a renal biopsy was

not performed. Considering the severity of progressively worsening underlying glomerular disease and the relatively early gestational age, we proposed steroid treatment in order to reduce proteinuria and informed her about the risks and advantages of the treatment. She agreed to steroid treatment and received an intravenous methylprednisolone pulse followed by 50 mg of oral prednisolone. Urinary protein excretion increased progressively at 8.0 g/day despite steroid treatment, and the fetus died in utero 8 days after the initiation of treatment. She delivered a small-for-gestational age male fetus (birth weight 350 g) with no gross congenital abnormalities. Placental pathology showed no obvious thrombosis or infarction. There was no evidence of a molar pregnancy.

A percutaneous renal biopsy was performed for diagnosis at 13 days postpartum. On light microscopy, there were 24 glomeruli, none of which showed global or segmental sclerosis. Capillary lumens were narrowed due to endothelial cell swelling (Fig. 2a). Segmental double contours with mesangial cell interposition were also present. Glomeruli were slightly enlarged, often pouting into the proximal tubules (Fig. 2b). Glomerular thrombosis was not observed. Immunofluorescence studies showed significant IgM and trace fibrinogen deposits along the peripheral capillary loop (Fig. 2c). Electron microscopy demonstrated that endothelial cells were swollen and had lost their fenestrations (Fig. 2d, e). Podocyte foot processes were well preserved despite heavy proteinuria. Because these findings confirmed a diagnosis of preeclampsia, steroid treatment was discontinued.

Fig. 2 Renal biopsy findings consistent with preeclampsia in the healing stage. **a** The glomerulus shows endothelial cell swelling and narrowed capillary lumen. The glomerular basement membrane demonstrates segmental double contours with mesangial interposition. (Periodic acid-methenamine-silver stain, scale bar 100 μ m), **b** the enlarged glomerulus shows herniation of the tip into the proximal tubule (“pouting”, arrow). (Periodic acid-Schiff stain, scale bar 100 μ m), **c** an immunofluorescence micrograph shows positive

staining for IgM along the inside of the capillary wall. (scale bar 100 μ m), **d** electron microscopy image shows endothelial cell swelling. Vacuolation is seen in the cytoplasm of glomerular endothelial and epithelial cells. (original magnification $\times 1,840$), **e** swollen endothelial cells show enlarged subendothelial spaces and loss of fenestrations. Note the well-preserved podocyte foot processes (original magnification $\times 5,750$)

Her blood pressure returned to normal within a few weeks after delivery and she was tapered off antihypertensive drug therapy. Urinary protein excretion decreased to 1.3 g/day 1 month postpartum, and fell to normal levels within 6 months postpartum.

Discussion

There is general agreement that new onset of proteinuria with hypertension before the 20th week of gestation strongly suggests underlying renal disease rather than preeclampsia, because preeclampsia rarely occurs before that time [2–4]. However, the treatment of a pregnant woman with a suspicion of glomerular disease is still based on sporadic clinical experiences because evidence is scant [5]. The relative risks and benefits of empirical treatment have to be considered carefully in each case. In the present case, we made an initial tentative diagnosis of underlying glomerular disease based on the onset gestational age (18 weeks) and considered the rapidly worsening nephrotic

syndrome severe enough to warrant steroid treatment. However, the patient received a final diagnosis of preeclampsia occurring before the 20th week of gestation based on the after-delivery course and renal biopsy findings. The incorrect tentative diagnosis in this case was attributable to a gestational age at presentation inconsistent with the definition of preeclampsia and to the lack of a renal biopsy during the pregnancy.

Preeclampsia is traditionally defined as new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive patient [1]. However, recent data suggest that preeclampsia may develop before 20 weeks, after 48 h postpartum or in the absence of typical symptoms of hypertension or proteinuria. These cases are termed as atypical preeclampsia [6]. Development of preeclampsia before 20 weeks of gestation usually accompanies partial molar pregnancy with triploidy or antiphospholipid syndrome [6–9]. Preeclampsia not associated with these disorders before 20 weeks of gestation is considered to be rare. This would seem to be an accurate assertion, as a literature search identified only 4

Table 1 Case reports of preeclampsia before 20 weeks of gestation without trophoblastic diseases or antiphospholipid syndrome

Case	Hazra et al. [10]	Imasawa et al. [11]	Stillman et al. [12]	Maya et al. [13]	Present case (2014)
Age (years)	41	35	30	17	30
Gestational age at the onset (weeks)	18	15	15	19	18
Parity	3	0	0	0	0
Risk factors of PE	Previous PE Age >40	Nulliparity Twin pregnancy	Nulliparity Twin pregnancy	Nulliparity	Nulliparity
Urinary protein excretion (g/day)	9	16	3.7	1.8	8.0
Renal biopsy	Not done	17 weeks	15 weeks	Antepartum	Postpartum
Light microscopy	–	Endotheliosis Mes interposition Mesangiolysis	Endotheliosis	Endotheliosis Mes interposition Pouting	Endotheliosis Mes interposition Pouting
IF microscopy	–	IgM (peri) Fibrin (subendo)	IgM, κ , λ (peri) Fibrin (peri)	NA	IgM (peri) Fibrinogen ($\pm$)
Electron microscopy	–	EDD (–) FP preserved	EDD (–) FP preserved	EDD (–) Focal FP effacement	EDD (–) FP preserved
Obstetric outcome	Termination	Termination	Termination	Termination	IUFD
Comorbidity	–	Uterus myoma	PCOS	–	–
Past history	Hyperthyroidism	–	–	–	–

PE preeclampsia, *Mes* mesangial, *IF* immunofluorescence, *IgM* immunoglobulin M, *peri* peripheral pattern, *subendo* subendothelial pattern, *NA* not available, *EDD* electron dense deposit, *FP* foot process, *IUFD* intrauterine fetal death, *PCOS* polycystic ovary syndrome

published cases [10–13]. Clinical and pathologic characteristics of these cases and the present case are summarized in Table 1. Based on the available data, it would seem that these cases do share some features. In general, risk factors for preeclampsia include advanced maternal age (>40 years), nulliparity, a large placenta (twin pregnancy), previous preeclampsia, a family history of preeclampsia, obesity, and preexisting medical conditions, including hypertension, chronic kidney disease, diabetes, and thrombotic vascular diseases [14]. All 5 cases included 1 or more risk factors. Specifically, 4 cases involved nulliparous women and 2 cases involved women who were pregnant with twins. The onset of preeclampsia revealed bimodal peaks at 15 and 18–19 weeks of gestation, and the 2 cases with twin pregnancy had earlier onset. All but 1 case presented with nephrotic syndrome. Renal biopsies were performed in 3 cases during pregnancy and in the present case after delivery. All biopsies revealed glomerular capillary endotheliosis, but did not show evidence for focal segmental glomerulosclerosis that can accompany the glomerular endotheliosis of preeclampsia [15]. In all cases, hypertension and proteinuria improved after medical termination or delivery.

Preeclampsia and underlying renal disease share similar clinical and laboratory findings but require different treatments. A critical clinical decision is required, especially in early pregnancy when fetal growth and maturity are insufficient for survival outside of the uterus, as to whether the pregnancy should be continued or terminated. Therefore, the accurate distinction between preeclampsia and underlying renal disease is imperative, although often difficult on clinical grounds.

Uterine or umbilical artery Doppler velocimetry is used in the prediction and diagnosis of preeclampsia. The transformation of subplacental arteries is normally complete at 20–24 weeks of gestation [16]. Impedance in the uterine artery decreases gradually during vessel transformation and is stable after 24 weeks of gestation in normal pregnancy [17, 18]. Increased uterine artery impedance beyond 20–24 weeks of gestation has been reported to reflect abnormal placentation and relate to the development of preeclampsia [19]. However, it may be difficult to interpret the results of uterine artery impedance before 20 weeks of gestation.

Biomarkers in maternal blood such as soluble frn-like tyrosine kinase-1 (sFlt-1) or placental growth factor (PlGF) have been reported to be helpful in diagnosing

preeclampsia [20]. The abnormal placenta, known to play a central role in the pathogenesis of preeclampsia, secretes excessive sFlt-1 into the maternal blood. This heightened level of sFlt-1 binds PlGF and vascular endothelial growth factor (VEGF), prevents their interaction with endothelial cell-surface receptors, and results in endothelial cell dysfunction. Increased levels of sFlt-1 and decreased free PlGF have been reported in women with preeclampsia as compared with healthy pregnant women. Unfortunately, methodologies for the measurements of these biomarkers have not been covered yet by health insurance and not available for clinical use at present in Japan. They may prove to be useful in the future for distinguishing preeclampsia from underlying renal disease if changes in these biomarkers are evaluated in pregnant women with renal disease.

Although performing a renal biopsy during pregnancy is still controversial, it may be helpful in confirming the diagnosis. However, we did not perform a renal biopsy during pregnancy in the present case. Generally, in pregnant women with new onset of hypertension, aggressive blood pressure reduction could be harmful for the fetus and a reasonable goal is recommended to be systolic pressure between 140 and 160 mmHg and diastolic pressure between 90 and 100 mmHg by Japan Society for the Study of hypertension in pregnancy. On the other hand, increased blood pressure (systolic pressure >140 mmHg or diastolic pressure >90 mmHg) was an independent predictor of post-biopsy bleeding complications [21]. Therefore, we considered this patient at higher risk for biopsy-related bleeding. A recent systematic review, however, demonstrated no statistically significant association between hypertension and post-biopsy bleeding complications [22]. Moreover, according to another systematic review, no severe biopsy-related bleeding complications were recorded in early pregnancy from 0 to 21 weeks of gestation [5]. The systematic review also indicated that renal biopsy results led to therapeutic changes in 66 % of cases. Collectively, renal biopsy may be considered as safe and useful tool for differential diagnosis between preeclampsia and underlying renal disease before 20 weeks of gestation.

In conclusion, this report demonstrates that preeclampsia can occur before the 20th week of gestation in the absence of molar pregnancy with triploidy or antiphospholipid syndrome. Even before 20 weeks of gestation, preeclampsia should be considered in the differential diagnosis in pregnant women presenting with new onset of hypertension with proteinuria, especially in the presence of any risk factors for preeclampsia. In this setting, renal biopsy may be considered as an option for definitive diagnosis to guide decisions pertaining to appropriate patient management.

Conflict of interest The authors have declared that no conflict of interest exists.

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