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Efficacy of expectant management of severe preeclampsia and preeclampsia superimposed on chronic hypertension before 34 weeks gestation

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ABSTRACT

Objectives: To investigate the effect of chronic hypertension on expectant management for preeclampsia (PE).
Study design: Pregnant women who were diagnosed with severe PE before 34 weeks of gestation between 2005 and 2016 and managed at a tertiary center were the subjects of the study. Mothers were classified into two groups: a severe superimposed PE (SSP) group and a severe PE (SP) group. We compared the groups in terms of perinatal outcomes.
Main outcome measures: Pregnancy prolongation from the diagnosis of severe PE to delivery.
Results: The SSP group included 30 women whereas the SP group included 79 women. Expectant management could be performed in 24 subjects (80.0%) in the SSP group and 49 (62.0%) in the SP group (P = 0.110). Gestational age at diagnosis of PE (P = 0.016) and gestational age at delivery (P = 0.031) were significantly lower in the SSP group than in the SP group. There were no significant differences between the groups in terms of pregnancy prolongation (SSP, 8.5 days versus SP, 6.0 days; P = 0.25) or maternal and neonatal complications.
Conclusions: Compared to severe PE, severe PE superimposed on chronic hypertension does not increase the prevalence of maternal complications, and an equivalent pregnancy prolongation was obtained. Expectant management was possible in severe superimposed PE on chronic hypertension, as it was in severe PE.

1. Introduction

Expectant management is recommended in patients with severe preeclampsia (PE) at < 34 weeks of gestation, provided the maternal and fetal conditions are stable, considering the poor prognosis and perinatal deaths associated with premature infants [1–4]. Expectant management of PE superimposed on chronic hypertension and/or renal disease is equally recommended in patients with severe PE at < 34 weeks of gestation from the viewpoint of preventing complications due to infant prematurity. However, reports on the extent to which pregnancy prolongation can be expected in PE superimposed on chronic hypertension and the effect that chronic hypertension has on expectant management of PE are sparse [5].

We have compared the differences in maternal and perinatal outcomes after expectant management of patients with severe PE and severe PE superimposed on chronic hypertension to investigate the effect of chronic hypertension on expectant management for PE.

2. Materials and methods

Pregnant women who developed severe PE before 34 weeks of gestation, between 2005 and 2016 at the Yokohama City University Medical Center, were the subjects of the study. This study was approved by the ethics committee of the Yokohama City University Medical Center (B170900032).

Those who could be managed expectantly for at least 48 h were enrolled in the expectant manageable group. Mothers were classified into two groups: a severe superimposed PE (SSP) group and a severe PE (SP) group based on the status of coexisting chronic hypertension. We compared pregnancy outcomes between both groups with pregnancy prolongation as the primary outcome.

Severe PE was defined as hypertension with a systolic blood pressure of at least 160 mmHg and/or diastolic blood pressure of 110 mmHg with concurrent proteinuria of at least 300 mg/day, renal insufficiency, liver involvement, neurological complication, or hematological complication. Renal insufficiency was defined as a serum creatinine level

Abbreviations: PE, Preeclampsia; SSP, Severe superimposed preeclampsia; SP, Severe preeclampsia

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Table 1
Maternal background and reasons for diagnosing PE between both groups.

	SSP (N = 30)	SP (N = 79)	P value	Odds ratio	95% CI
Maternal age	36 (27–43)	35 (19–45)	0.17		
Nulliparous	21 (70%)	43 (54.4%)	0.19	0.51	0.21–1.26
Pre-pregnancy BMI	26.6 (17.4–38.6)	21.6 (16.0–32.7)	< 0.001		
BMI at delivery	29.0 (20.7–38.9)	24.8 (17.9–36.4)	< 0.001		
Use of antihypertensive drugs before 20 weeks of gestation	17 (56.7%)				
Entry criteria for preeclampsia					
Proteinuria	28 (93.3%)	75 (94.9%)	0.67	0.75	0.13–4.31
Liver involvement	5 (16.7%)	17 (21.5%)	0.79	0.73	0.24–2.19
Hematological complications	2 (6.5%)	5 (6.3%)	1.00	1.06	0.19–5.77
Renal insufficiency	2 (6.7%)	5 (6.3%)	1.00	1.06	0.19–5.77
Neurological complication	0 (0%)	1 (1.3%)	1.00	–	–

SSP: Severe superimposed preeclampsia.
SP: Severe preeclampsia.
BMI: Body mass Indice.

Table 2
The percentage of subjects in the expectant management possible group and the reason for terminating the pregnancy of the subjects in the expectant management impossible group.

	SSP (N = 30)	SP (N = 79)	P value	Odds ratio	95% CI
Expectant management	24 (80.0%)	49 (62.0%)	0.11	2.45	0.90–6.68
Reasons for judging expectant management impossible					
NRFS	3 (10%)	21 (26.6%)	0.38	0.43	0.07–2.54
Placental abruption	1 (3.3%)	9 (11.4%)	0.66	0.47	0.05–4.58
Uncontrollable hypertension	2 (6.7%)	4 (5.1%)	0.26	3.3	0.44–23.94
HELLP syndrome	0 (0%)	5 (6.3%)	0.56	–	–
Neurological complication	0 (0%)	1 (1.3%)	1.00	–	–

SSP: Severe superimposed preeclampsia; SP: Severe preeclampsia.
NRFS: Non reassuring fetal status.
HELLP: Hemolysis, elevated liver enzymes, and low platelet.

exceeding 1.1 mg/dL. Liver involvement was defined as elevated transaminase levels and/or severe right hypochondrial or epigastric pain, and neurological complications as eclampsia, restlessness, impaired vision, stroke, hyperreflexia, or severe headache. Hematological complications were defined as a platelet count below 100,000/μL, disseminated intravascular coagulation, or hemolysis. Chronic hypertension was defined as hypertension that was diagnosed before pregnancy or hypertension that existed before 20 weeks gestation. Pregnant women with congenital abnormality of the fetus, multiple pregnancy, uncertain gestational age, secondary hypertension, or complications such as idiopathic thrombocytopenic purpura were excluded from the study.

The post-hospitalization management was similar to that previously reported [6]. Delivery was performed when the symptoms below were detected during the expectant management or at 34 weeks of gestation. The criteria for terminating pregnancy based on the maternal indications were as follows: 1) failure of blood pressure control despite administration of antihypertensive medications at adequate doses; 2) eclampsia and imminent eclampsia, impaired vision, and persistent, severe headache; 3) hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; 4) pulmonary edema; 5) acute renal failure (serum creatinine level increased by at least 1.0 mg/dL from baseline); and 6) placental abruption. The criteria for terminating pregnancy based on the fetal indications were as follows: 1) abnormal fetal heart rate showing repeated late decelerations or severe variable decelerations in the form of traditional non-stress test (NST); 2) biophysical profile score ≤4; and 3) reversed end-diastolic flow in the umbilical artery at or after 32 weeks of gestation. In all women diagnosed with severe superimposed PE (SSP) for which expectant management was performed, pregnancies were terminated at 34 weeks of gestation. We administered magnesium sulfate for all patients in both groups during labor or cesarean section, and this was continued for 24 h after delivery. We also administered magnesium sulfate to patients who developed cerebral or visual symptoms related to preeclampsia, such as eclampsia, a severe headache, or scotoma.

We investigated the primary endpoint, which was pregnancy prolongation from the diagnosis of severe PE to delivery, and the secondary endpoints, which were maternal background, gestational age at the diagnosis of severe PE, gestational age at delivery, birthweight of neonate, Apgar score, umbilical artery blood pH, neonatal intensive care unit (NICU) admission rate, cesarean delivery rate, and maternal and neonatal complications. The gestational age at onset of severe PE was defined as the gestational age at which the above criteria for the diagnosis of severe PE were met. The maternal complications investigated were liver involvement, hematological complications, and composite morbidity. Composite morbidity included one or more of the following conditions: renal insufficiency, pulmonary edema, eclampsia, HELLP syndrome, and placental abruption. Grade III or IV intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), chronic lung disease (CLD), and necrotizing enterocolitis (NEC) were evaluated as neonatal complications. Neonatal complications, or fetal and neonatal death within 28 days of birth were handled as composite neonatal morbidity.

The data are presented as medians (range) or frequencies (percentage). JMP pro (version 12.2.0, SAS Institute, Cary, NC, USA) was used for statistical analyses. We applied the Mann-Whitney *U* test for determining coefficients of variation. Fisher's exact tests were used to detect differences in categorical data by group. The level of statistical significance was set at $P < 0.05$.

3. Results

Table 1 presents the maternal characteristics and entry criteria for PE in the SSP and SP groups. Of the subjects who developed severe PE

Table 3
Maternal background and pregnancy outcomes of the expectant management possible group.

	SSP (N = 24)	SP (N = 49)	P value	Odds ratio	95% CI
Maternal age	35.5 (27–41)	36 (19–45)	0.89		
Nulliparous	20 (83.3%)	29 (59.2%)	0.062	0.29	0.09–0.98
Pre-pregnancy BMI	27.4 (18.9–37.9)	21.5 (16.0–32.7)	< 0.001		
BMI at delivery	29.6 (20.7–38.9)	25.4 (18.1–36.1)	< 0.001		
Gestational age at onset of severe preeclampsia (weeks)	27.4 (21.3–33.4)	29.3 (23.7–33.6)	0.016		
Gestational age at delivery (weeks)	28.8 (24.7–34.0)	30.3 (24.1–34.0)	0.031		
Pregnancy prolongation	8.5 (2–30)	6.0 (2–36)	0.25		
Cesarean delivery	24 (100%)	49 (100%)	–		
NRFS	9 (37.5%)	24 (49.0%)	0.46	0.61	0.23–1.70
Use of intravenous calcium channel blocker	12 (54.6%)	10 (45.5%)	0.015	3.9	1.35–11.25
Maternal outcome					
Liver involvement	8 (33.3%)	14 (28.6%)	0.79	1.25	0.44–3.58
Hematological complications	0 (0%)	3 (6.1%)	0.55		
Maternal composite morbidity	4 (16.7%)	19 (38.8%)	0.066	0.32	0.093–1.07
Renal insufficiency	0 (0%)	2 (4.1%)	1.00		
Pulmonary edema	0 (0%)	3 (6.1%)	0.55		
Eclampsia	0 (0%)	2 (4.1%)	1.00		
HELLP syndrome	2 (8.3%)	7 (14.3%)	0.71	0.55	0.10–2.85
Placental abruption	2 (8.3%)	7 (14.3%)	0.71	0.55	0.10–2.85
Neonatal outcome					
Birth weight	969 (422–1544)	1046 (444–1930)	0.19		
Perinatal mortality	0 (0%)	0 (0%)	–		
Apgar scores at 5 min < 7	1 (4.2%)	9 (18.3%)	0.093	0.19	0.02–1.62
UmApH < 7.1	2/20 (10.0%)	8/43 (18.6%)	0.48	0.49	0.09–2.53
NICU admission	24 (100%)	48 (98.0%)	1.00	–	–
Composite neonatal morbidity	11 (45.8%)	12 (24.5%)	0.11	2.61	0.93–7.33
IVH	1 (4.2%)	2 (4.1%)	1.00	1.02	0.09–11.9
PVL	0 (0%)	0 (0%)	–		
CLD	11 (45.8%)	11 (22.9%)	0.06	2.85	1.00–8.11

SSP: Severe superimposed preeclampsia; SP: Severe preeclampsia.
BMI: Body Mass Indice.
HELLP: hemolysis, elevated liver enzymes, and low platelet.
Note: Maternal complications were defined as renal insufficiency, pulmonary edema, HELLP syndrome, eclampsia, or placental abruption.
IVH: Intraventricular hemorrhage, PVL: Periventricular leukomalacia, CLD: Chronic lung disease.
Perinatal mortality: Fetal or neonatal death between 22 weeks of gestation and 28 days after birth.
Composite neonatal morbidity: IVH, PVL, or CLD.

at < 34 weeks of gestation, 30 had chronic hypertension and was assigned to the SSP group and 79 without chronic hypertension were assigned to the SP group. In the SSP group, body mass indices (BMIs) before pregnancy and at delivery were significantly high. The entry criteria for PE did not differ between the two groups. In the SSP group, 17 (56.7%) patients used antihypertensive drugs before 20 weeks of gestation. A low dose of aspirin was used by only one patient in the SSP group for recurrent miscarriage. No patient used low-dose aspirin for prevention of PE.

Table 2 presents the percentages of subjects in whom expectant management could be performed for at least 48 h and the relevant reasons for those subjects in whom expectant management was impossible. Expectant management could be performed in 24 subjects (80.0%) in the SSP group and 49 (62.0%) in the SP group, showing no significant difference between the two groups (P = 0.110). Of the reasons for the termination of pregnancy within 48 h in those subjects for whom expectant management was impossible, after being diagnosed with severe PE or severe superimposed PE, placental abruption, non-reassuring fetal status (NRFS), and poor blood pressure control were common in both groups. The reasons for judging expectant management impossible for a subject did not differ between the two groups.

Table 3 presents the maternal characteristics and pregnancy outcomes of the subjects in the SSP and SP groups in whom expectant management could be performed. Maternal age and primipara rate showed no difference between the two groups. BMI was significantly higher in the SSP group before pregnancy and at delivery. With regard to pregnancy outcome, gestational age at diagnosis of PE was significantly lower in the SSP group than in the SP group (P = 0.016). Moreover, gestational age at delivery was also significantly lesser in the SSP group (P = 0.031). The median duration by which pregnancy was prolonged was 8.5 days (range, 2–30 days) in the SSP group and 6.0 days (range, 2–36 days) in the SP group, showing a tendency to be longer in the SSP group; however, there was no significant difference between the groups (P = 0.245). The rate of intravenous calcium channel blocker use was higher in the SSP group than in the SP group (P = 0.015).

Maternal composite morbidity was 4/30 (16.7%) in the SSP group and 19/49 (38.8%) in the SP group, showing that it tended to be common in the SP group; however, there was no significant difference between both groups. In addition, with regard to neonatal composite morbidity, it was 11/30 (45.8%) in the SSP group where gestational age at delivery was low and 11/49 (22.9%) in the SP group, showing that it tended to be common in the SSP group. There was no significant difference between the two groups in terms of neonatal composite morbidity, and there were no still births or neonatal deaths in both groups.

4. Discussion

In the SSP group, both the gestational age at diagnosis and delivery were significantly lower than those in the SP group. In addition, co-existing chronic hypertension had no effect on the expectant management of PE, and there was no difference between the two groups regarding pregnancy prolongation. Moreover, the incidence of maternal and neonatal complications was not different between the two groups.

Pregnancy was prolonged by a median of 8.5 days (range, 2–30 days) in the SSP group and 6.0 days (range, 2–36 days) in the SP group, showing no significant difference between the groups. Similarly, expectant management was possible in both the SSP and SP groups. To

date, studies investigating whether the presence of chronic hypertension affects the expectant management of PE are limited to the one study reported by Paulino et al. (5). They performed expectant management for at least 48 h after subjects diagnosed with severe PE at 24–33 weeks of gestation were hospitalized. When pregnancy prolongation was investigated in 29 subjects in the SSP group and 100 in the SP group, the duration of pregnancy was reported to be prolonged by a median of 8.5 ± 5.2 and 8.4 ± 5.6 days, respectively, showing no difference between the groups. They set proteinuria as an essential parameter in the definition of PE, and even then, there was no contradiction with the results of our study, where proteinuria was not set as an essential parameter of PE.

In the SP and SSP groups, there was no difference in the frequency of maternal and neonatal complications. The onset of various complications, including placental abruption, is reported to increase in patients with PE [7–9]. Similarly, the risk of onset of complications, such as placental abruption, is reported to increase with superimposed PE [10,11]. In this study, the rate of intravenous calcium channel blocker use was higher in the SSP group, but there was no difference between the SSP and SP groups regarding incidence of maternal complications. Similarly, there was no difference between the SSP and SP groups regarding incidence of neonatal complications. These results agree with those reported by Paulino et al. [5] and indicate that the presence of chronic hypertension does not affect expectant management for PE.

This study is a single-center retrospective study, and detailed follow-up of the contents of the patients' chart was possible. Importantly, the subjects were the same patients who underwent pregnancy and delivery managed by the same protocol. The major limitation of this study is the small sample size. To avoid this limitation, it is preferable to accumulate a larger number of subjects to investigate whether the presence of chronic hypertension from 20 weeks gestation and earlier affects the pregnancy and delivery management of PE. In this study, only one patient took low-dose aspirin for recurrent miscarriage. The administration of aspirin in low doses for the prevention of PE was not a standard practice in Japan during the study period; however, in recent years, this is followed worldwide, and such administration of aspirin may have an effect on pregnancy prolongation.

5. Conclusions

Compared to severe PE with no coexisting chronic hypertension, severe PE superimposed on chronic hypertension does not increase the prevalence of maternal complications, and an equivalent pregnancy prolongation could be obtained. Expectant management was possible in superimposed PE on chronic hypertension, as it was in severe PE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.01.007.

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