COMMITTEE REPORT

Pregnancy outcomes in Japanese pregnant women with either chronic hypertension or white coat hypertension (JP-WCH): protocol for a prospective multicenter cohort study

Chikako Hirashima¹, Kayo Takahashi¹, Shigeru Saito², Hiroyuki Seki³, Kazushi Watanabe⁴, Katsuhiko Naruse⁵, Shintaro Makino⁶, Hirohito Metoki⁷, Shigeki Matsubara¹, Atsuhiro Ichihara⁸, Akihide Ohkuchi¹

¹Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Tochigi, Japan, ²Department of Obstetrics and Gynecology, Graduate School of Medicine and Pharmaceutical Science for Research, University of Toyama, Toyama, Japan, ³Department of Obstetrics and Gynecology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, ⁴Department of Obstetrics and Gynecology, Aichi Medical University School of Medicine, Aichi, Japan, ⁵Department of Obstetrics and Gynecology, Nara Medical University, Nara, Japan, ⁶Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan, ⁷Division of Public Health, Hygiene and Epidemiology, Tohoku Medical and Pharmaceutical University, Sendai, Japan, ⁸Department of Medicine II, Endocrinology and Hypertension, Tokyo Women’s Medical University, Tokyo, Japan

It is not known whether pregnant women with chronic hypertension (CH) develop preeclampsia (PE) more frequently than those with white coat hypertension (WCH). Therefore, we planned the following 2 studies: study 1 is a multicenter prospective observational study to distinguish WCH and CH, in (A) pregnant women with suspected hypertension with blood pressure measured in a clinical setting, and who had not been diagnosed with hypertension prior to the current pregnancy, and (B) pregnant women with a previous diagnosis of hypertension, but who have not received an accurate diagnosis specifying whether they have CH or WCH; study 2 is a multicenter retrospective cohort study, which will start after the recruitment of subjects in study 1, to compare the incidences of PE and gestational hypertension (GH) in women with WCH or CH. Here, we described a protocol for a prospective multicenter cohort study (JP-WCH study; UMIN study ID: UMIN000032790).

Introduction

It is not known whether pregnant women with chronic hypertension (CH) develop preeclampsia (PE) more frequently than those with white coat hypertension (WCH).¹,² Therefore, we planned the following 2 studies: study 1 is a multicenter prospective observational study to distinguish WCH and CH, in (A) pregnant women with suspected hypertension with blood pressure measured in a clinical setting, and who had not been diagnosed with hypertension prior to the current pregnancy, and (B) pregnant women with a previous diagnosis of hypertension, but who have not received an accurate diagnosis specifying whether they have CH or WCH; study 2 is a multicenter retrospective cohort study, which will start after the recruitment of subjects in study 1, to compare the incidences of PE and gestational hypertension (GH) in women with WCH or CH. Here, we described a protocol for a prospective multicenter cohort study (JP-WCH study; UMIN study ID: UMIN000032790).
gestational hypertension (GH), and related diseases of hypertensive disorders of pregnancy (HDP) in women with WCH or CH, after detecting all women with CH and/or WCH at < 20 weeks of gestation that occurs during 1st Apr. 2018 to 31st Mar. 2020.

The two above-mentioned studies may reveal the incidence rates of PE (including superimposed PE) and GH in women with WCH in the first half of pregnancy. In addition, they could reveal whether pregnant women with WCH develop PE less frequently than those with CH. These results may suggest the necessity of discriminating WCH from CH in pregnant women with suspected hypertension. The current classification of HDP by the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) includes CH, but not WCH. If our studies reveal that the incidence rates of PE are similar between women with CH and those with WCH, we should consider the inclusion of WCH in the HDP classification in the future. Thus, the current studies are relevant, because they will generate very important clinical data to facilitate decision-making regarding hypertension in pregnant women.

Materials and methods

Study ID: RinDai17-173, approved by Jichi Medical University Institutional Review Board on 18th May, 2018.

Study type

[Study 1] A multicenter prospective observational study.  
[Study 2] A multicenter retrospective cohort study.

Primary outcomes

PE (including superimposed PE)

Secondary outcomes

GH, gestational proteinuria, eclampsia, HELLP syndrome, acute fatty liver of pregnancy (AFLP), posterior reversible encephalopathy syndrome (PRES), aggravation of hypertension, pulmonary edema, placental abruption, disseminated intravascular coagulation syndrome (DIC), intracranial hemorrhage, labor onset hypertension, puerperal period onset hypertension, intrauterine fetal death at 12 to 21 weeks of gestation, abortion at 12 to 21 weeks of gestation (not including stillbirth), stillbirth at 22 and/or later than 22 weeks of gestation, extremely low birth weight infant, very low birth weight infant, low birth weight infant, non-reassuring fetal status (NRFS), fetal growth restriction (FGR), small-for-gestational-age (SGA) infant, light-for-gestational-age (LGA) infant, early neonatal death (END), perinatal death (PD), neonatal death (ND), discharge with infant death, extremely preterm birth, very preterm birth, preterm birth at <35 weeks of gestation, preterm birth, cesarean delivery, emergent cesarean delivery, and maternal death.

Subjects

[Study 1] Inclusion criteria are as follows: pregnant women aged between 16 and 59 years old at < 19 weeks of gestation during 1st Apr. 2018 to 31st Mar. 2020, (A) who show suspected hypertension with blood pressure measured in a clinical setting, but had not been diagnosed with hypertension prior to the current pregnancy, and (B) who have previous diagnosis of hypertension, but who have not received an accurate diagnosis specifying whether they have CH or WCH. Exclusion criteria are as follows: pregnant women whose inclusion in this study is deemed difficult by research investigators, or pregnant children going to elementary or junior high school.

[Study 2] Inclusion criteria are as follows: pregnant women aged between 16 and 59 years old at < 19 weeks of gestation during 1st Jan. 2018 to 31st Dec. 2020, who have been diagnosed with CH or WCH. Exclusion criteria are as follows: pregnant women who do not provide consent for either study 1 or study 2, or pregnant children going to elementary or junior high school.

Definition of PE, GH, superimposed PE (SPE)

PE is defined as hypertension accompanied by proteinuria exceeding 30 mg/24 h that emerges for the first time after 20 weeks of gestation, but both symptoms normalize by 12 weeks postpartum. In addition, the following cases are also classified as PE: hypertension emerges for the first time after 20 weeks of gestation, with an impaired liver function, renal insufficiency, neurological complications, or hematological complications, even if there is no proteinuria. Moreover, the following case is also classified as PE: hypertension emerges for the first time after 20 weeks of gestation, with uteroplacental insufficiency, such as FGR, an abnormal umbilical artery flow velocity waveform, or stillbirth.

GH is diagnosed in women with hypertension for the first time during pregnancy, but without proteinuria, and hypertension that normalizes by 12 weeks postpartum.

Superimposed PE (SPE) is diagnosed in the following four cases: (1) new onset of proteinuria in hypertensive women who have no proteinuria before 20 weeks of gestation; (2) hypertensive women with an impaired liver function, renal insufficiency, neurological complications, or hematological complications, even if there is no proteinuria; (3) hypertensive women with uteroplacental insufficiency, such as FGR, an abnormal umbilical artery...
flow velocity waveform, or stillbirth; (4) hypertension and proteinuria documented antecedent to pregnancy and/or detected before 20 weeks of gestation, with one or both progressing after 20 weeks of gestation; (5) renal disease with proteinuria documented antecedent to pregnancy and/or detected before 20 weeks of gestation, accompanied by a new onset of hypertension after 20 weeks of gestation.

**Definition of CH and WCH using HBPM and/or ABPM**

In this study, we will measure clinic blood pressure using an automated digital oscillometric sphygmomanometer three times consecutively at 15-sec intervals after 1 to 2 minutes’ rest in a waiting room, when a pregnant woman shows hypertension (either systolic blood pressure [SBP] for the first time ≥ 140 mmHg, or diastolic blood pressure [DBP] for the first time ≥ 90 mmHg). We suspect hypertension based on the clinic blood pressure in the following cases: 1) the mean SBP of clinic blood pressure on the second and third measurements ≥ 140 mmHg, or 2) the mean DBP of clinic blood pressure on the second and third measurements ≥ 90 mmHg. When we suspect hypertension, we recommend the pregnant woman to measure HBP for 7 days to rule out WCH, and instruct her to come to the out-patient clinic 7 days after the first day of suspected hypertension, and to measure her blood pressure consecutively three times in the waiting room in the hospital. Hypertension is diagnosed when the pregnant woman repeatedly showed either SBP ≥ 140 mmHg (the mean value of the second and third measurements) or DBP ≥ 90 mmHg (the mean value of the second and third measurements) on 2 occasions ≥ 4 hours apart. When a pregnant woman has suspected hypertension, but hypertension changed to normal blood pressure at the next visit, without showing repeatedly hypertension thereafter, we diagnosed her with normal blood pressure.

Criteria for hypertension by HBPM and ABPM during pregnancy and the puerperal period are as follows: 1) for HBPM, hypertension is defined as a mean SBP ≥ 135 mmHg and/or mean DBP ≥ 85 mmHg using blood pressures measured in the morning and at bedtime for 7 days (The Japanese Society of Hypertension Guidelines for the Management of Hypertension [JSH 2014]),4) 2) for ABPM, hypertension is defined as a) 24-hour (h) SBP ≥ 130 mmHg and/or 24-h DBP ≥ 80 mmHg, b) daytime SBP ≥ 135 mmHg and/or daytime DBP ≥ 85 mmHg, c) night-time SBP ≥ 120 mmHg and/or night-time DBP ≥ 70 mmHg (JSH 2014).4) To discriminate WCH from CH, we defined hypertension by clinic blood pressure, in addition, hypertension by HBPM and/or ABPM.4) If pregnant women in the first half of pregnancy show hypertension by clinic blood pressure, but they were not evaluated by HBPM and/or ABPM, we do not classify such women as having either WCH or CH, and just observe them with suspected hypertension. In women with a past history of either essential hypertension or WCH diagnosed before the current pregnancy, we adopt the same diagnosis in the current pregnancy.

**Setting of target sample size**

Brown et al. reported that 22% of pregnant women with CH developed PE, whereas 8% of pregnant women with WCH developed PE.1) Thus, the incidence rate of PE in women with CH was significantly higher than in those with WCH (P = 0.008).1) However, in our previous preliminary cohort study in a tertiary center in Japan, 21% of pregnant women with CH developed PE, whereas 15% of pregnant women with WCH developed PE.2) Therefore, we could not identify a significant difference in the incidence rate of PE between women with CH and those with WCH.2) Using these two results, we estimated that PE occurs in pregnant women with CH at a rate of 21.5% (means of 22 and 21%, respectively), whereas PE occurs in pregnant women with WCH at a rate of 11.5% (means of 8 and 15%, respectively) in the general population. To evaluate the following hypothesis: pregnant women with CH develop PE more frequently than those with WCH, it was determined that a total of 472 subjects should be recruited, under the conditions of alpha error of 5% and beta error of 20%. We also estimated that almost 25% of the recruited subjects would be lost during maternal checkup. Therefore, we finally determined 630 subjects (315 for CH, and 315 for WCH) as an appropriate target sample size.

**Statistics**

We will compare the incidence rate of PE in pregnant women with CH and WCH using Fisher’s exact test. Next, using the completely followed up subjects and censored cases, we will compare the occurrence of PE using Kaplan-Meier analysis. Finally, we will compare WCH and CH while adjusting for other risk factors for PE, such as age, obesity, a past history of PE/GH, primiparity, smoking, complication of diabetes mellitus, multiple pregnancy, and assisted reproductive technology, using multivariate logistic regression analysis.

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Conflict of interest
None.

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