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Pregnancy-induced hypertension is associated with maternal history and a risk of cardiovascular disease in later life: A Japanese cross-sectional study

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ABSTRACT

Objective: To clarify the associations between pregnancy-induced hypertension (PIH) with heritability of PIH from mother to daughter and the risk of cardiovascular disease in later life in Japanese women. Study design: The Japan Nurses' Health Study (JNHS) is a cohort study of Japanese women's health. Data from the JNHS baseline survey between 2001 and 2007 were used to conduct a cross-sectional analysis. Of the 49,927 respondents in the baseline survey, 10,456 parous women who were \geq 45 years old at baseline were included in the analysis.

Main outcome measures: The age-adjusted odds ratio (OR) of PIH in women whose mother had a history of PIH, and the age-adjusted OR of PIH in participants for hypertension, hypercholesterolemia and diabetes mellitus (DM).

Results: The age-adjusted OR of PIH was 2.72 (95% confidence interval [CI]: 2.14–3.46) in women whose mother had a history of PIH compared with those whose mother did not have PIH. PIH was a risk factor for hypertension (age adjusted OR: 2.85, 95% CI: 2.45–3.11), hypercholesterolemia (age-adjusted OR: 1.49, 95% CI: 1.29–1.72) and DM (age-adjusted OR: 1.53, 95% CI: 1.11–2.11), as determined by logistic regression analysis.

Conclusions: In Japanese women, the risk of PIH is approximately 2.7-fold greater in those whose mothers also had PIH compared with those whose mothers did not. PIH is a risk factor for hypertension, hypercholesterolemia, and diabetes mellitus in later life.

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1. Introduction

Pregnancy-induced hypertension (PIH) is a common condition that is typically associated with trophoblast and vascular endothelial disorders [1–3]. The underlying mechanisms of PIH are complex and are likely to be multifactorial, including insulin resistance [4], hyperlipidemia [5], hypercoagulability [6], inflammation [7], and a hyperdynamic circulation [8]. PIH may increase the risk of "metabolic syndrome" and cardiovascular disease later in life either via a shared cause or subclinical vascular damage, which occurs during PIH [9–12]. Intriguingly, the offspring of a pregnancy

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affected by PIH will also have increased blood pressure during childhood and nearly double the risk of stroke in later life [13–18]. We hypothesized that the intergenerational similarities in risk profiles substantiate the developmental origin of vascular risk factors in women with a history of pregnancies complicated by PIH.

Hypertension, hyperlipidemia, and diabetes mellitus (DM) are common in Japan and are the main risk factors for cardiovascular disease. An adverse outcome in pregnancy may be an indicator of increased risk of metabolic and vascular diseases in later life [19]. Therefore, a history of PIH may be an independent risk factor for diseases that in turn increase cardiovascular risk in the long term. Moreover, precise quantification of the increased risk of cardiovascular disease in mid-life in women affected by PIH affords the opportunity to intervene with preventative therapies at an earlier age than usual. Therefore, if PIH is a risk factor for cardiovascular disease later in life, it may have implications for health promotion in women, where follow up and counseling of women with a

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history of PIH may offer a window of opportunity in which to prevent future disease.

This study aimed to clarify the associations between PIH with heritability of PIH from mother to daughter, and the risk of cardio-vascular disease in later life in Japanese women.

2. Materials and methods

2.1. Definition of PIH in this study

A wide range of terminology and diagnostic criteria has been used over the years to classify hypertensive disorders of pregnancy and define pre-eclampsia. Several internationally recognized definitions are available, but at present there is no universal classification system or definition for pre-eclampsia. Hypertensive disorders of pregnancy have four defined categories: (i) gestational hypertension; (ii) pre-eclampsia and eclampsia; (iii) superimposed pre-eclampsia; and (iv) chronic hypertension. Gestational hypertension is diagnosed in women whose blood pressure is ≥140/90 mmHg after the 20th gestational week, regardless of proteinuria. Women with a blood pressure \geq 140/90 mmHg or proteinuria either before the 20th gestational week or 12 weeks after delivery are excluded because of the possibility that they may have had latent hypertension or renal disease [20]. Pre-eclampsia is characterized by de novo hypertension and proteinuria, and is a major cause of maternal and fetal morbidity and mortality worldwide [21]. The minimum criteria for pre-eclampsia are the presence of gestational hypertension and proteinuria, which is defined as 24-h urinary protein excretion exceeding 300 mg or persistent presence of \geq 30 mg/dl of protein (+1 dipstick) in random urine samples. In this study, PIH was defined as gestational hypertension or preeclampsia.

2.2. Study design and data source

The Japan Nurses' Health Study (JNHS) is a large-scale, nationwide, prospective cohort study investigating the lifestyle habits and health of Japanese women by following female nurses aged ≥25 years for at least 10 years [22]. The JNHS was designed to be comparable with the Nurses' Health Study (NHS). The objectives of the JNHS are to monitor the occurrence of various diseases prospectively, including female-specific diseases, and to assess the effects of various lifestyle factors and healthcare habits on the health of Japanese women. The JNHS mainly consists of a crosssectional baseline survey and longitudinal follow-up surveys. A cross-sectional baseline survey was conducted between 2001 and 2007. A total of 49,927 female nurses aged ≥25 years throughout Japan replied and completed the baseline health questionnaires. Of the respondents, approximately 15,000 women agreed to participate in the follow-up surveys. This program of research was conducted in accordance with the international guidelines of Good Epidemiology Practice and Japanese Ethical Guidelines for Epidemiological Research. The institutional review board of Gunma University and the National Institute of Public Health reviewed and approved the study protocol. Participants were informed of the purposes and procedures of the study in an invitation letter, and all of the signed consent forms were sent to the INHS coordination center. Basic information on medical, anthropometric, reproductive, and dietary factors, including body weight, history of oral contraceptive use, cigarette smoking, alcohol consumption, parity, and age at menarche, was collected by means of self-administered questionnaires at the baseline survey.

With regard to PIH, women were asked in the baseline survey: "Have you suffered from PIH? (yes/no)". If the answer was yes, we inquired about the age at the time of PIH. We also inquired

about the maternal PIH history at the participant's birth. With regard to hypertension, DM, and hypercholesterolemia (serum total cholesterol ≥240 mg/dl), women were asked: "Have you ever been diagnosed by a medical doctor? (yes/no)". If the answer was yes, we enquired about treatment and the age at diagnosis. We also inquired about the parental history of hypertension and DM. Body mass index (BMI) was calculated as weight/height² (kg/m²). Smoking history was determined via the question: "Have you smoked more than 20 packs of cigarettes in your life?" If the answer was yes, we inquired whether the participant "currently smokes" or "smoked in the past, but quit". The frequency of alcohol consumption was determined according to the following seven categories: "none", "1–2 times per month", "once a week", "2 days per week", "3–4 days per week", "5–6 days per week", and "every day".

2.3. Study population and statistical analysis

Of the 49,927 respondents in the baseline survey, 33,083 women were parous. A total of 25,958 parous women provided information regarding their history of PIH. Of the 25,958 women, 10,456 women who were \geq 45 years at the time of the baseline survey were analyzed for the risk of heritability of PIH from the mother, and associations with hypertension, DM, and hypercholesterolemia that developed during middle-age.

The prevalence of PIH and its 95% confidence interval (CI) were calculated. The risk ratio (RR) and its 95% CI were estimated to evaluate the risk of PIH in women whose mothers had a history of PIH compared with those whose mothers did not. Unconditional logistic regression models were used to estimate the age-adjusted odds ratio (OR) and the 95% CI for the risk of PIH in women whose mothers had a history of PIH compared with those whose mothers did not. Multivariable logistic regression was also performed to adjust for potential confounding variables, including age at survey, presence of PIH in the mother, number of deliveries, current BMI, and parental history of hypertension. Unconditional logistic regression models were also used to estimate age-adjusted ORs and 95% CIs for the association of PIH of participants with hypertension, DM and hypercholesterolemia. Multivariable logistic regression was performed to adjust for potential confounding variables, including age at survey, PIH among participants, current BMI, smoking, and alcohol consumption. In these models, we categorized women according to current BMI (i.e., BMI < 18.5, BMI ≥ 18.5 and <25.0, BMI \geq 25.0 and <30.0, and BMI \geq 30), smoking (i.e., never, past, and current), and alcohol consumption (i.e., none, less than 1 day a week, 1 or 2 days, and 3 days or more a week). P < 0.05 was considered statistically significant. All statistical analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

The characteristics of the study population (n = 10,456) and risk of PIH for the women enrolled in this study are shown in Table 1.

The prevalence (95% CI) of PIH in women whose mothers had a history of PIH at the participant's birth and in women whose mothers did not have PIH was 26.7% (22.2–31.6%; 97/363 women) and 11.8% (11.1–12.4%; 1188/10,093 women), respectively. The RR (95% CI) of PIH in women who had a maternal history of PIH compared with those that did not was 2.27 (95% CI; 1.90–2.71). The age-adjusted OR of PIH in women who had a maternal history of PIH compared with those that did not was 2.72 (95% CI: 2.14–3.46), and the multivariable-adjusted OR was 2.98 (95% CI: 2.25–3.95, Table 2).

Of the 10,456 parous women who were \geq 45 years at the time of the baseline survey, 1219 (11.7%), 274 (2.6%), and 1904 women (18.2%) had been diagnosed with hypertension, DM, and hypercholesterolemia, respectively. For hypertension, the age-adjusted

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