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Serum cobalt status during pregnancy and the risks of pregnancy-induced hypertension syndrome: A prospective birth cohort study

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ABSTRACT

Cobalt (Co) is an essential trace element and has been suggested to be involved in blood pressure regulation, but few studies have focused on serum Co status during pregnancy and the risks of pregnancy-induced hypertension syndrome (PIH). The aim of this study was to prospectively assess the association between serum Co levels during pregnancy and the risks of PIH, and to explore how the maternal Co status contributes to the incidence of PIH. 3260 non-hypertensive women before pregnancy with singleton births in Ma'anShan birth cohort study (MABC) were recruited with the assessment of maternal Co concentrations, additionally, the levels of 7 inflammatory factors and 3 stress factors in placentas were also determined. Relative risks (RRs) [95% confidence intervals (CIs)] for the risks of PIH were assessed and the relationships between 10 factors and maternal Co status during pregnancy were evaluated as well. A total of 194 (5.95%) women were diagnosed with PIH. The concentrations of Co varied from the first trimester to the second trimester, and maternal serum Co concentrations during pregnancy were negatively associated with the incidence of PIH in a linear fashion. There was a clear trend in RRs according to decreasing exposure to Co levels in the second trimester (RR^a = 1.80, 95% CI (1.26, 2.56); RR^b = 1.73, 95% CI (1.21, 2.46) and RR^c = 1.43, 95% CI (1.02, 2.04) when low Co levels comparing with high Co levels before and after adjustment for confounders; and RR^a = 1.29, 95% CI (0.88, 1.88); RR^b = 1.28, 95% CI (0.87, 1.87) and RR^c = 1.25, 95% CI (0.86, 1.82) when medium Co levels comparing with high Co levels before and after adjustment for confounders). In addition, the trend for the first trimester was nearly identifical to those for the second trimester (RR^a = 1.35, 95% CI (0.94, 1.93); RR^b = 1.33, 95% CI (0.93, 1.91); RR^c = 1.22, 95%CI (0.86, 1.73) when low Co levels comparing with high Co levels before and after adjustment for confounders; and RR^a = 1.10, 95% CI (0.76, 1.60); RR^b = 1.13, 95% CI (0.77, 1.64) and RR^c = 1.12, 95% CI (0.77, 1.63) before and after adjustment for confounders). Interestingly, Co concentrations in the second trimester were also inversely associated with the levels of some inflammatory factors and all three stress factors in placentas. This prospective study suggested that lower maternal serum Co concentration in the second trimester may associate with the incidence of PIH in Chinese population. Additionally, the maternal Co concentrations in the second trimester could reduce inflammatory and oxidative damage to the placenta. Further evidence is needed to support the findings and assess the mechanisms underlying the association.

1. Introduction

Pregnancy-induced hypertension syndrome (PIH), which includes gestational hypertension, pre-eclampsia, eclampsia and HELLP syndrome, is a life-threatening disease during pregnancy and remains a leading cause of maternal and perinatal morbidity and mortality worldwide [1,2]. Hypertension is common during pregnancy, several pregnant women may have their blood pressure recorded as above the normal at some point before delivery, and there is a widespread geographic, social, economic and racial variation in its incidence [3,4]; pre-

Abbreviations: CI, confidence interval; Co, cobalt; PIH, pregnancy-induced hypertension syndrome; MABC, Ma'anshan birth cohort; Ca, calcium; Mg, magnesium; KED, kinetic energy discrimination

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eclampsia, which is defined as hypertension accompanied by proteinuria, complicates about 2%-8% of pregnancies [5]; serious and rare complications include eclampsia and HELLP syndrome, which associate with an increased risk of maternal death [3]. Due to the improved antenatal care, the incidence of pre-eclampsia has declined in developed countries, however, the incidence remains high in developing countries [6]. In 2011, the national survey showed that the incidence of PIH is 5.22% in China [7]. Not only PIH could cause adverse birth outcomes, accumulating evidences have also indicated a consistent association between pre-eclampsia and long-term harmful effects, such as offsprings' cognitive function, cardiovascular disease and type 2 diabetes [8–12]. Thus, the underlying mechanism and etiology for PIH is of great concern.

Essential trace elements play important roles in various biological processes of human bodies. Homeostasis of trace elements, which are maintained through tightly regulated mechanisms of uptake, storage and secretion, is therefore vital for life, especially for those pregnant women [13–18]. Cobalt (Co), as an essential component of vitamin B12, is required in humans and a number of animals for keeping healthy. Human exposure to Co often occurs via dietary sources [19]. Previous study has shown that it was involved in blood pressure regulation [20], whether it has any effect on the incidence of PIH, few studies have focused on it.

Therefore, we have undertaken a large well-characterized prospective cohort study to address (a) whether maternal Co status during pregnancy is associated with the risk of PIH, and (b) whether there is a critical period in this relationship because the concentrations of Co varied during the different trimester and (c) how the maternal Co status contributes to the incidence of PIH.

2. Material and methods

2.1. Study population and recruitment

The subjects of the present study were from the Ma'anshan Birth Cohort (MABC) study, a prospective cohort study designed to examine the relationship between prenatal exposure and outcomes, such as pregnant outcomes, child health and development. Pregnant women, when they came to Maternal and Child Health Care Centre in Ma'anshan for their first prenatal checkup in early pregnancy were consecutively recruited from May 2013 to September 2014, in addition, the women should be ≥18 years old and ≤14 gestational weeks. A total of 3474 pregnant women were recruited for this birth cohort. A face-to-face interview were performed by trained investigators using three different questionnaires in the first, second, third trimester of pregnancy (about 10, 26 and 34 gestational weeks, respectively) to collected data, and maternal blood samples were also obtained simultaneously. Detailed procedures of pregnant women recruitment and of blood sampling are described elsewhere [21,22].

For this analysis, eligible participants were women who were still participating in the research when delivery and delivered a live singleton. In our study, 120 spontaneous miscarriages, 2 ectopic pregnancies, 10 stillbirths, 30 inducing labors, 39 pregnant women giving birth to twins, 7 pregnant women without PIH information, 6 having chronic hypertension prior to 14 weeks but not developing into pre-eclampsia, eclampsia, or HELLP syndrome were all excluded. Additionally, 291 women who did not provide blood samples or whose samples were exhausted by our team's other researches in the first trimester, and 162 women without blood samples with the same reason in the second trimester were excluded. Accordingly, 2969 pregnant women in the first trimester, 3098 pregnant women in the second trimester were eligible for our study. According to pregnant women's medical records, there were 169 and 184 women with PIH (gestational hypertension or pre-eclampsia) respectively (Fig. 1).

Oral and written consents were acquired from all participants. The recruitment and subsequent follow-up protocols (including the serum analysis of Co and measurement of inflammatory factors and stress factors in placentas) were both approved by the ethical committee of Anhui Medical University (Ethical approval code: 20131195).

2.2. Definition of PIH

Pregnancy-induced hypertensive syndrome (PIH) was the outcome we intended to investigate, including gestational hypertension, pre-eclampsia, eclampsia, and HELLP syndrome. Pregnant women, if the physician made the clinical diagnosis and recorded it in their anamnesis, were recognized to have gestational hypertension, pre-eclampsia, eclampsia or HELLP syndrome. In addition, reference to a recent study performed by Werner EF [23], we recognized a woman to have gestational hypertension if either of her blood pressure values in the second and third trimester (26 and 34 weeks approximately) satisfy at least one of the situations described below: elevated diastolic blood pressure (> 90 mm Hg) at both measurements, elevated systolic blood pressure (> 140 mm Hg) at both measurements, or elevated diastolic blood pressure at one measurement and elevated systolic blood pressure at the other measurement. Additionally, women could not be recorded as a patient with PIH even though their two blood pressure values ≥140/90 before 14 weeks (chronic hypertension) if they did not develop into pre-eclampsia, eclampsia or HELLP [23].

2.3. Confounding variables

The detailed information we collected included pregnant woman's age, pre-pregnancy BMI, education level, parity, gravidity, smoking, alcohol consumption, social-economic status.

Pregnant woman's age and pre-pregnancy BMI were treated as continuous variables in all the statistical models. Parity status was defined as primiparous or multiparous, and gravidity status was defined as primigravida or multigravida. Pre-pregnancy BMI was calculated according to self-reported weight and height measurement before conception. Smoking during pregnancy and stopping smoking at any stage of pregnancy were both considered as maternal smoking during pregnancy. Due to the influence of Chinese traditional culture, there were only a few of samples with drinking during pregnancy, we did not consider this confounding variable into statistical analysis. Additionally, the serum concentrations of calcium and magnesium during pregnancy were also considered as confounders [24].

2.4. Measurement of Co, Ca and Mg in maternal serum

Maternal fasting blood samples at about 10 and 26 gestational weeks were collected in the morning and then were poured into metal-free polypropylene (PP) tubes. We centrifuged PP tubes for 15 min at 3500 rpm to separate out the serum. The sera were stored at −80 °C until be analyzed. Before analysis, all sera should be placed on a specimen rocker for at least 1 h. Serum Co concentration was determined by ICP-MS (Perkin Elmer NexION 350X, Shelton, CT, USA) according to the method we established previously [25]. Briefly, the maternal serum was diluted 1:25 with a diluent which contains 1% double-distilled HNO_3 and 0.05% Triton®X-100. Co^{59}, Ca^{43} and Mg^{25} were selected as the isotopes of our targeted analytes and Y as their internal standard element. The instrumentation conditions were detailed in our previous study [25]. KED mode was used to eliminate the polyatomic ion interference and matrix-matched protocol was used to eliminate mass matrix interference. Each sample was analyzed three times. The detection limit of the method for Co, Ca and Mg were 0.053 μg/L, 1.11 mg/L and 17.5 μg/L respectively. The precision for inter-day and intra-day determinations for Co, Ca and Mg were 10.29% and 11.44%, 0.73% and 4.36%, and 0.49% and 3.36% respectively. In addition, we used the certified reference materials from Seronorm to perform daily quality control (LOT: 1309438).