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High serum iron level is associated with an increased risk of hypertensive disorders during pregnancy: a meta-analysis of observational studies

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ABSTRACT

The exact cause of hypertensive disorders in pregnancy (HDP) has not been clearly elucidated. Some researchers have recently investigated the relationship between the serum iron level and the incidence of HDP. However, the results are inconsistent, and these data have not been systematically evaluated. Therefore, we conducted a meta-analysis to evaluate the real association between the serum iron level and the incidence of HDP. We searched for published and ongoing trials in PubMed, EMBASE, Scopus, Web of Science, the Chinese Biomedical Database, CNKI, and the WANFANG database from January 1990 to May 2015 to identify studies that met our predefined criteria. Finally, 26 studies, including 1 cross-sectional study, 23 case-control studies, and 2 prospective nested case-control studies, including 1349 patients and 1119 control participants, were selected for this meta-analysis. The pooled results show that a high serum iron level increased the incidence of HDP (standard mean deviation [SMD], 1.50; 95% confidence interval [CI], 0.94-2.06; $P < .0001$), especially gestational hypertension (SMD, 3.65; 95% CI, 1.50-5.81; $P = .0009$) and preeclampsia (SMD, 1.27; 95% CI, 0.76-1.78; $P < .0001$). No significant difference was seen between the eclampsia groups and the control participants (SMD, 3.34; 95% CI, −0.02 to 6.69; $P = .05$). The results of this meta-analysis indicate that a high serum iron level is associated with an increased risk of HDP, especially gestational hypertension and preeclampsia.

1. Introduction

Hypertensive disorders in pregnancy (HDP) are a group of diseases that includes gestational hypertension (GH), preeclampsia, and eclampsia. *Gestational hypertension* is defined as newly developed hypertension with a blood pressure greater than 140/90 mm Hg after 20 weeks of gestation in a previously normotensive woman [1]. Preeclampsia is a combination of GH and proteinuria that is diagnosed by a finding of at least 300 mg of protein in a 24-hour urine sample. Severe preeclampsia involves a blood pressure greater than 160/110 mm Hg with additional medical signs and symptoms

Abbreviations: CI, confidence interval; GH, gestational hypertension; HDP, hypertensive disorders in pregnancy; HIF, hypoxia-inducible factor; SMD, standard mean deviation.

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[1,2]. Preeclampsia can occasionally progress to a life-threatening condition called eclampsia, which is a hypertensive emergency that can lead to several serious complications including vision loss, brain swelling, seizures or convulsions, kidney failure, pulmonary edema, and disseminated intravascular coagulation [1,2].

Globally, approximately 10% of pregnancies are complicated by HDP [3]. In the United States, HDP affect approximately 8% to 13% of pregnancies [1], and these rates are higher in the developing world [1]. Preeclampsia occurs in 2% to 8% of pregnancies and is one of the leading causes (approximately 16%) of maternal and perinatal morbidity and mortality [3-5]. Some studies have shown an association between HDP and an increased risk of adverse maternal and neonatal outcomes, including maternal death, infants born small for their gestational age, and preterm and fetal growth restriction [1,6,7].

Studies have shown that oxidative stress may contribute to the pathogenesis of HDP [8-11]. Iron, a redox-active transition metal that is significant in the generation of free radicals, is involved in the nitrosylation and oxidation processes in patients with preeclampsia [12,13], but the exact cause has not been clearly elucidated. In recent years, some researchers have investigated the involvement of iron in the cause of HDP [12,14-18]; nevertheless, the results are inconsistent. For example, Fenzl et al [12] reported that serum iron levels measured at 20 weeks of gestation were significantly higher in pregnant women with preeclampsia than in normotensive pregnant women. This result is mostly in agreement with those of previous studies by Zargar et al [19], Kim et al [14], and Siddiqui et al [20]. However, the findings of a recent study by Tande et al [18] were quite different; the serum iron levels were lower in the GH group than in the control group, a result that was also demonstrated by Sarwar et al [16] and Rathore et al [21].

To our knowledge, there is still no consensus on this issue, and these data have not been systematically evaluated. Because iron is involved in the oxidation processes associated with the generation of oxygen free radicals [12,14,19,20], we hypothesized that a higher serum iron level increased the risk of HDP. With the increasing speculation regarding the involvement of trace elements, including iron, in the pathogenesis of HDP, the aim of this meta-analysis was to review the evidence from the previous studies and determine whether a higher serum iron level increases the risk of HDP.

2. Methods and materials

2.1. Search strategy

We searched PubMed, EMBASE, Scopus, Web of Science, the Chinese Biomedical Database, CNKI, and the WANFANG database for all published articles regarding human studies in female participants published in either English or Chinese with a study period between January 1990 and May 18, 2015. We used the following keywords: (1) iron OR ferrum OR ferrous OR ferric OR ferri- OR ferro- OR sidero- OR Fe; (2) pregnancy-induced hypertension OR gestational hypertension OR pregnancy hypertension OR mother hypertension OR maternal hypertension OR pre-eclampsia OR preeclampsia OR eclampsia OR hypertensive disorders in pregnancy; and (3) both (1) and (2). We also searched the references of all identified articles, as well as additional review articles, to find additional studies that had not been identified during the computerized search. If the same participants were enrolled in more than 1 study, we used the latest study with the largest number of participants.

2.2. Inclusion and exclusion criteria

Using the search criteria defined above, 135 publications were identified. Each manuscript was reviewed by 2 authors (Song QY and Luo WP) for the following inclusion criteria: (1) a study population of pregnant women; (2) data available to assess the association between the serum iron level and HDP; and (3) an appropriate control group. The articles were excluded if they met the following criteria: (1) inclusion of pregnant women who were HIV seropositive or who had active tuberculosis; (2) no available full text or eligible information; or (3) no control group.

2.3. Data extraction

The relevant data were extracted independently by 2 reviewers (Song QY and Luo WP), and disagreement was resolved by a third reviewer (Zhang CX). The following data were collected from each study: first author, year of publication, study design, country or region of study, period of study, type of HDP, participant numbers, selection of control participants, maternal age, gestational age at sampling, parity, and adjustment for confounders.

2.4. Assessment of study quality

The Newcastle-Ottawa Scale was independently used by 2 reviewers to assess the methodological quality of the case-control studies [22]. The scale consists of 9 items that cover 3 dimensions: (1) selection of cases and control participants (4 items); (2) comparability of cases and control participants based on the design or analysis (2 items); and (3) ascertainment of exposure for cases and control participants and the nonresponse rate (3 items). The total score ranges from 0 to 9, with higher scores indicating higher quality. In this study, a score greater than 7 was defined as high quality [22].

2.5. Statistical analyses

Most enrolled studies listed the means ± SD of the serum iron level, whereas some studies listed the means ± SEM; thus, we transformed SEMs to SDs with the following formula: $SEM = SD/\sqrt{n}$. If a study gave sample sizes, means, and SDs separately for patients with GH, preeclampsia, and eclampsia, we combined them into a single HDP group according to the recommendations outlined in the Cochrane Handbook [23].

Standard mean deviations (SMDs) and 95% confidence intervals (CIs) were used as the effect size of the serum iron levels. The SMDs were calculated by the mean difference between the case and control groups by the pooled SDs. The heterogeneity of the SMDs across studies was tested by means of the Q statistic (significance level at $P < .05$). A P value of greater than .05 on the Q test indicates little variation between the studies; in this case, a fixed-effect model was