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Early pregnancy maternal trace mineral status and the association with adverse pregnancy outcome in a cohort of Australian women

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ABSTRACT

Maternal micronutrient deficiencies in pregnancy can have profound effects on fetal development and pregnancy outcome. Plasma trace minerals including copper, zinc, selenium and iron have been shown to be extremely important in supporting reproduction. We sought to determine whether there is an association between maternal trace mineral status in early pregnancy and pregnancy complications using a prospective cohort study of 1065 pregnant Australian women who were recruited as part of the Screening for Pregnancy Endpoints (SCOPE) study in Adelaide. Copper, zinc, selenium and iron present in the plasma were measured using mass spectrometry in samples collected at 15 ± 1 weeks' gestation. After adjusting for covariates, women with lower plasma copper (< 27.9 μmol/L and 27.9–32.5 μmol/L) had decreased risk for any pregnancy complication when compared with women with high plasma copper (> 32.5 μmol/L) (aRR = 0.87; 95% CI = 0.76, 0.99 and aRR = 0.88; 95% CI = 0.78, 1.00, respectively). This was also observed when adjusting for plasma zinc and selenium status (< 27.9 μmol/L: aRR = 0.81; 95% CI = 0.69, 0.96 and 27.9–32.5 μmol/L: aRR = 0.84; 95% CI = 0.72, 0.98). Combined low copper and zinc status was also associated with a reduced risk of any pregnancy complication as compared with high copper and zinc status (aRR = 0.80; 95% CI = 0.70, 0.93). These results provide justification for further work into elucidating the mechanistic role of trace elements in early pregnancy, as well as their interactions in supporting successful pregnancy outcomes.

Maternal nutrient stores and diet supply all the macro- and micronutrients to support optimal fetal growth essential for successful pregnancy [1]. Hence, it is not surprising that maternal deficiencies in key micronutrients can have profound effects on fetal development and pregnancy outcome [2]. Pregnancy complications including pre-eclampsia (PE), gestational diabetes mellitus (GDM), spontaneous preterm birth (sPTB) and fetal growth restriction (FGR) together affect 25% of first pregnancies and predict lifelong morbidity and mortality for both the mother and infant [3]. Furthermore, micronutrient deficiencies which tend to be associated with decreased consumption of foods rich in micronutrients, have also been associated with the development of PE, GDM, sPTB, FGR, as well as gestational hypertension (GH) [2].

Extensive investigations into micronutrient deficiencies have focused on those common within pregnant populations including folate and vitamin D [4]. However, evidence is emerging about the importance of trace minerals like iron, zinc and copper in supporting successful pregnancy [5]. It is known that trace minerals are crucial for the maintenance of cell proliferation and function with severe deficiencies in copper and zinc during pregnancy having been shown to have a teratogenic effect on the fetus [6]. This is likely driven by a reduction in the activity of key enzymes which require these metals structurally in order to function, as well as compromised oxidant defence systems [6]. It is also important to acknowledge the importance of micronutrients in mediating inflammation and the immune response. Animal models of iron, copper and zinc deficiencies have been shown to be associated with compromised immunity and increased susceptibility to infection [7]. Pregnancy complications including PE and FGR have been associated with increased oxidative stress and circulating markers of inflammation [8,9] and therefore there may be a causal connection

Abbreviations: FGR, fetal growth restriction; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, preeclampsia; sPTB, spontaneous preterm birth; SGA, small-for-gestational age

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between micronutrient deficiencies in pregnancy and the development of pregnancy complications mediated by oxidative stress and inflammation.

The association between trace minerals and pregnancy have been described previously [10–17], however many of these studies have been conducted in late pregnancy or at term. Given that many of these pregnancy complications originate in early gestation, it is important to also understand how micronutrient status in the first trimester is associated with adverse pregnancy outcomes. Marginal micronutrient deficiencies early in pregnancy may lead to more severe deficiencies later in pregnancy due to increased metabolic demands from the rapidly growing placenta and fetus. Thus we aimed to determine whether deficiencies in the trace minerals copper, zinc, selenium and iron at 15 ± 1 weeks' gestation may be associated with a number of pregnancy complications. As copper and zinc share similar electro-chemical properties and biological pathways [18], we also explored interactions between zinc and copper status in early pregnancy and their relationship with adverse pregnancy outcomes with the goal of better understanding how these minerals may be important to successful pregnancy.

1. Materials and methods

1.1. Study participants

Plasma samples were obtained from Adelaide participants recruited as part of the international prospective Screening for Pregnancy Endpoints (SCOPE) study. Nulliparous women carrying a singleton pregnancy were recruited at 15 ± 1 weeks' gestation from the Lyell McEwin Hospital, Adelaide, Australia between November 2004 and September 2008. Ethics approval was gained from the University of Adelaide ethics committee and all women provided written consent (approval no: REC 1712/5/2008). At recruitment, women were interviewed by a research midwife and asked questions on maternal demographics and had physical measurements recorded. These included age, body mass index (BMI) and smoking status [19]. Biochemical markers were also measured at 15 ± 1 weeks' gestation and included plasma C-reactive protein (CRP) [20]. Women were not eligible to participate in the study if they suffered from a pre-existing medical condition or had obstetric history which placed them at high risk of developing PE, sPTB or delivering a small-for-gestational age (SGA) infant. Those who had suffered three or more miscarriages or had undergone three or more pregnancy terminations were also excluded.

Uncomplicated pregnancies were defined as those without any pregnancy disorder and included normotensive women who delivered an appropriate weight for gestational age infant at term (≥37 weeks' gestation) [21]. GH was diagnosed as the development of high blood pressure (systolic blood press ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) on at least two occasions after 20 weeks' gestation. PE was defined as GH in conjunction with proteinuria (24 h urinary protein ≥300 mg or a spot urine protein:creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥2) or any multisystem complication of PE or uteroplacental dysfunction [22]. GDM was diagnosed according to the International Associations of Diabetes and Pregnancy Study Groups criteria [23]. sPTB was defined as the spontaneous onset of labour at < 37 weeks' gestation. SGA was defined as birth weight below the 10th customised centile adjusted for maternal height, booking weight, ethnicity, delivery gestation and infant sex.

1.2. Elemental analysis

Venous blood samples were provided at 15 ± 1 weeks' gestation and collected into heparinised tubes in order to obtain plasma samples and then analysed using inductively-coupled plasma mass spectrometry (ICP-MS) (Agilent 7700 ICP-MS) (Agilent 5100 ICP-OES; CSIRO Analytical Services, South Australia) to measure the concentrations of copper, selenium, iron and zinc. Prior to analysis, 250 μL of plasma was digested in concentrated nitric acid (0% HNO_3) in sealed Teflon containers for approximately 48 h and then diluted. Samples were run alongside two internal standards: iridium and rhodium (Choice Analytical) at a concentration of 200 ppb and an 8-point calibration, including blank, was carried out between 0.01 μg/L and 100 μg/L. There were 47 (4.4%) women with plasma iron levels below the detection limit of 7.16 μmol/L and were therefore assigned 7.15 μmol/L.

1.3. Statistical analysis

All statistical analysis was performed in R (v3.1.1) [24]. Baseline characteristics were tested for normality using the Shapiro-Wilk test and summarised according to pregnancy outcome. Fisher's exact tests were performed for categorical variables and Welch's *t* test for continuous variables comparing women with each pregnancy complication to all other women. Plasma copper, zinc, selenium and iron were expressed as mean (± standard deviation: SD) and compared between women who developed a pregnancy complication and those who did not using a non-parametric Mann-Whitney *U*. Spearman's correlations were used to examine the relationship between each of the trace minerals with each other, as well as with circulating CRP; a marker of inflammation.

In order to assess the effects of each trace mineral on pregnancy outcome, plasma copper, zinc, selenium and iron were divided into tertiles based on their distribution amongst all women in this study. Relative risks (RR) and 95% confidence intervals (CIs) of pregnancy complications from any complication, PE, GH, GDM, sPTB and SGA for copper, zinc, selenium and iron were examined using multivariable Poisson regression with robust variance estimation. Multivariable adjustment was made for maternal age, maternal BMI and smoking status at 15 ± 1 weeks' gestation (yes compared to no) as covariates. Maternal socioeconomic status, determined by assigning the New Zealand socioeconomic index score (SEI) [25], was initially included in the adjusted model but did not change any effects observed and was subsequently removed in the final analyses. The final analyses were also repeated for copper, zinc and selenium adjusting for each other as well as covariates previously mentioned.

2. Results

Of the 1165 SCOPE women recruited in Adelaide, 1065 (91%) plasma samples from 15 ± 1 weeks' gestation were available for analysis of trace minerals. These included 558 (52%) women whose pregnancies were uncomplicated, 85 (8%) who later developed PE, 108 (10%) who were diagnosed with GH, 51 (5%) who were diagnosed with GDM, 65 (6%) who delivered spontaneously preterm and 134 (13%) who delivered an SGA infant. Mean maternal age and BMI for all women whose plasma was analysed was 23.71 ± 5 years and 27.01 ± 6.52 kg/m^2 (Table 1). Compared to those whose pregnancies were uncomplicated, women who went on to have a pregnancy complication had a higher BMI in early pregnancy but there was no difference in maternal age, smoking status or use of supplements at 15 ± 1 weeks' gestation.

Plasma trace minerals in all women ranged from 10.3 to 52.99 μmol/L for copper, 3.24–34.70 μmol/L for zinc, 0.253–1.785 μmol/L for selenium and 7.14–72.60 μg/L for iron. Mean plasma copper at 15 ± 1 weeks' gestation was higher in women who went onto have a pregnancy complication when compared to those whose pregnancies remained uncomplicated (Table 1; $P < 0.001$). Moderate differences in circulating levels of zinc, selenium and iron were also observed in the women who later developed a pregnancy complication compared to those who did not (Table 1). Circulating copper was positively correlated with both zinc (Supplementary Fig. 1A; $R^2 = 0.263$) and selenium (Supplementary Fig. 1B; $R^2 = 0.303$) but negatively correlated with iron (Supplementary Fig. 1C; $R^2 = -0.156$). Iron on the other hand, was positively