Journal of Trace Elements in Medicine and Biology 50 (2018) 139–145

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Nutrition

Amniotic fluid minerals, trace elements, and prenatal supplement use in humans emerge as determinants of fetal growth

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ARTICLE INFO

Keywords:
Ultrasound measurements
Minerals
Trace elements
Prenatal supplements
Amniotic fluid

ABSTRACT

Amniotic fluid (AF), which is swallowed by the developing fetus, contains minerals and trace elements, but their association with fetal growth has not been explored. Our objectives were to assess (1) whether concentrations of AF minerals and trace elements were associated with changes in 5 fetal ultrasound measurements (estimated weight, bi-parietal diameter, head circumference, abdominal circumference, femur length) between 16–20 and 32–36 wks gestation and (2) whether a prenatal supplement was associated with concentrations of AF minerals and trace elements or the 5 fetal ultrasound measurements. We measured, using inductively coupled plasma-mass spectrometry (ICP-MS), 15 minerals and trace elements (aluminum, arsenic, calcium, chromium, copper, iron, lead, magnesium, nickel, potassium, rubidium, selenium, silver strontium, zinc) in amniotic fluid collected from 176 pregnant women undergoing age-related amniocentesis for genetic testing (15.7 ± 1.1 wks). AF mineral concentrations, prenatal supplement use, and determinants of ultrasound measurements during early and late pregnancy were used in models to assess their impact on change in fetal ultrasound measurements. Positive associations were identified for change in bi-parietal diameter with AF calcium, for change in head circumference with AF copper and nickel, and for change in femur length with AF selenium. Arsenic was negatively associated with estimated fetal weight, and this relationship was modified by prenatal supplement use. Additionally, AF chromium concentrations were lower in women taking prenatal supplements. In conclusion, AF minerals were associated with fetal ultrasound indices, supporting a biological role for calcium, copper, nickel and selenium in promoting *in-utero* fetal growth. Evidence of a mineral-vitamin interaction between arsenic and folic acid in prenatal supplements and mineral-mineral interaction between iron and chromium would suggest that attention be paid to mineral and trace element formulation of prenatal supplements.

1. Introduction

Amniotic fluid (AF), which is swallowed by the developing fetus, provides an important window for identifying nutrients directly available for fetal absorption and fetal growth [1]. Two recent studies have quantified minerals and trace elements in AF, one during early and one during late pregnancy [2,3], but these studies did not examine their relationships to fetal growth. Only one study has explored associations of AF minerals and trace elements with fetal ultrasound measurements noting that copper was positively and magnesium was negatively associated with nearly all of the 5 ultrasound measurements in early pregnancy [4]. None of these studies controlled for prenatal supplement use.

Prenatal supplementation is a common practice in developed countries and is often recommended to correct for suspected inadequate nutrient intakes [5]. Previous studies have examined single minerals, calcium [6] and zinc [7], with fetal ultrasound measurements, showing no associations with calcium and increased femur length with zinc supplementation. However, these studies did not consider the impact of prenatal supplements on amniotic fluid composition.

The primary objective of this study was to determine whether concentrations of AF minerals and trace elements were associated with changes in 5 fetal ultrasound measurements. A secondary objective was to determine whether a prenatal supplement was associated with AF concentrations of minerals and trace elements, or with further changes in fetal ultrasound measurements.

2. Materials and methods

2.1. Study design

To assess the association of AF minerals and trace elements with fetal growth, this prospective study collected AF samples (12–20 wks gestation) from 176 pregnant women (34–40 yrs) undergoing age-

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https://doi.org/10.1016/j.jtemb.2018.06.012
Received 15 March 2018; Received in revised form 4 June 2018; Accepted 15 June 2018

related amniocentesis, and 5 fetal ultrasound measurements (estimated weight, bi-parietal diameter, head circumference, abdominal circumference, and femur length) at two time periods for each participant: early gestation (16–20 wks) and late gestation (32–36 wks). To assess change in growth, differences for each ultrasound measurement were determined by subtracting the early gestation measurement from late gestation measurement. AF samples were analyzed for concentrations of 15 minerals and trace elements (aluminum, arsenic, calcium, chromium, copper, iron, lead, magnesium, nickel, potassium, rubidium, selenium, silver, strontium, zinc) using ICP-MS (Varian 820 ICP-MS, Analytik Jena, Jena, Germany). AF was stored at −80 °C until analysis for minerals and trace elements.

To explore the potential contribution of prenatal supplements to AF mineral and trace element concentrations, and to fetal ultrasound measurements, participants completed questionnaires at time of recruitment about early prenatal supplement use, and we completed medical chart reviews after delivery to assess supplement use during late gestation. Women were subsequently divided into 4 groups depending on the pattern of prenatal supplement use. During early gestation, mothers were subdivided into 2 groups: those who reported taking a prenatal supplement (YES) and those who did not report taking a prenatal supplement (NO) during the entire first 16–20 wks of pregnancy. During late gestation, mothers were subdivided into 4 subgroups: (1) YES or NO to indicate that the women either did or did not take a prenatal supplement throughout the entire pregnancy; (2) EARLY to indicate that women only reported taking a prenatal supplement at 16–20 wks of gestation and not at 32–26 wks of gestation, and (3) LATE to indicate women only reported taking a prenatal supplement at 32–36 wks and had not reported taking a prenatal supplement at 16–20 wks gestation.

2.2. Setting and recruitment of participants

From 2002–2005, older pregnant women (34–40 yrs) undergoing age-related amniocentesis at St Mary's Hospital Center in Montreal, QC, Canada were invited to participate. Ethical approval was obtained from the university's institutional review board and St Mary's Hospital Centre. Written consent to use remaining AF for this study and to have access to the maternal medical chart was obtained at the time of age-related amniocentesis.

Maternal characteristics confirmed through medical chart review included: age, height, pre-pregnancy weight, maternal pre-pregnancy BMI, ethnicity (Caucasian, Asian, African-Canadian, other), and parity. Fetal characteristics included infant sex and 5 ultrasound measurements: estimated weight, bi-parietal diameter, head circumference, abdominal circumference and femur length.

2.3. Inclusion/exclusion criteria

Inclusion criteria were women with singleton pregnancies, giving birth via vaginal delivery or caesarian section, an AF sample of ≥2 mL as a result of undergoing age-related amniocentesis (34–40 yrs), and with two ultrasound measurements, one taken at 16–20 wks gestation and another at 32–36 wks gestation recorded in the maternal medical chart. Exclusion criteria were an abnormal genetic test and a multiple birth pregnancy.

2.4. Description of prenatal multivitamin-mineral supplements

The majority of participants used one of two Canadian prenatal supplement brands (Brand A, Brand B) available at the time. Given the age of mothers (34–40 yrs), adequacy of supplementation was compared to Health Canada's RDA/AI for pregnant women 31–50 years old.

Regarding vitamin supplementation, the majority of vitamins exceeded the RDA/AI in Brand A and Brand B: Vitamin C (117%), Vitamin E (200%), folic acid (160%), niacin (117%), pantothenic acid (160%), thiamin (214–257%), riboflavin (214–242%) and pyridoxine (157–526%). Exceptions were biotin, which met 100% of the RDA/AI, while Vitamin A (58–78%) and Vitamin D (42–67%) did not meet the RDA/AI.

For minerals, iron and calcium were the only two included in all available prenatal supplements; however, supplementation was below 50% of the RDA/AI for calcium but met or exceeded 100% RDA for iron. Interestingly, calcium and iron were the only minerals in Brand B. Other minerals in Brand A included chromium, copper, iodine, magnesium, manganese, molybdenum, and zinc and beginning in 2004 selenium. In Brand A, supplementation was below 50% of the RDA/AI for iodine, magnesium, and selenium. Supplementation of chromium reached 83% of the RDA/AI, and supplementation of copper and zinc met or exceeded 100% RDA/AI.

2.5. ICP-MS analysis of AF minerals and trace elements

Samples were analyzed by ICP-MS using a Varian 820 ICP-MS (Analytik Jena; Jena, Germany), equipped with a Collision Reaction Interface. AF samples were digested in acid-rinsed polypropylene tubes (VWR metal-free VWR 89049-170) using an 0.50 mL AF and concentrated trace metal grade nitric acid (JT Baker) for 24 h at room temperature. Samples were then heated to 60 °C for 3 h and left to cool for 2 h. After cooling, nanopure water was added to reach a final volume of 15 mL. Blanks, standards, replicates and external quality control samples were digested within the same batch at a ratio of 1 for every 6 samples.

Reference samples were used to establish detection limits (μg/L) and recovery performance was assessed using a water sample from Environment Canada Proficiency Testing Program (Sample FPTM 101-7), and two biological reference materials: urine QM-U-Q1306 and serum QM-S-Q1104 samples from the Institut de Santé Publique du Quebec – Centre de Toxicologie. Recovery rates above 90% were recorded for aluminum, silver, arsenic, copper chromium, nickel, selenium, strontium, lead, and zinc and above 85% for iron and rubidium. Detection limits were: magnesium 2.47, arsenic 2.26, potassium 10.0, calcium 10.0, nickel 1.32, copper 3.15, zinc 1.80, rubidium 0.93, strontium 1.24, lead 0.81, chromium 1.17, arsenic 1.64, selenium 3.52. Aluminum and iron were within the range of other reports [2–4].

2.6. Statistical analysis

Statistical analysis was completed using PROC GLM in SAS 9.3. Classification variables for prenatal supplement groups were (No/Yes) at 16–20wks of gestation or (No/Early/Late/Yes) at 32–36 wks gestation). These patterns of prenatal supplement usage were adjusted in all statistical analyses. Other classifications variables included infant sex (female/male), parity (0, 1, 2, 3, 4+), and ethnicity (Caucasian, Asian, African-Canadian, other). Continuous variables were gestational wks between ultrasound measurements, pre-pregnancy BMI, maternal height, mineral and trace element concentrations, and changes in ultrasound measurements of fetal growth: estimated weight, bi-parietal diameter, head circumference, abdominal circumference, and femur length.

Given the absence of established determinants for ultrasound measurements with the exception of fetal weight, we performed a multiple linear regression analysis for each individual ultrasound measurement at 16–20 wks and again at 32–36 wks gestation. For these analyses, previously established determinants for infant birth weight were considered; these included gestational age, infant sex, pre-pregnancy BMI, parity, and mother's ethnicity [8]. Additionally, we tested week of amniocentesis, estimated weight (for all ultrasound measurements except estimated weight), pattern of prenatal supplement use, and maternal height for femur length. All final multiple linear regression models included prenatal supplement use, gestational age, and infant sex as well as any additional variable that entered a univariate model