Maternal & Child Nutrition

DOI: 10.1111/j.1740-8709.2012.00430.x

Original Article

Maternal selenium, copper and zinc concentrations in pregnancy associated with small-for-gestational-age infants

Hiten D. Mistry*, Lesia O. Kurlak†, Scott D. Young‡, Annette L. Briley*, Fiona Broughton Pipkin†, Philip N. Baker§ and Lucilla Poston*

**Division of Women's Health, King's College London, Women's Health Academic Centre, KHP, London, UK, †Department of Obstetrics & Gynaecology, School of Clinical Sciences, University of Nottingham, Nottingham, UK, ‡School of Biosciences, Faculty of Science, University of Nottingham, Nottingham, UK, and §Departments of Obstetrics/Gynecology & Physiology, University of Alberta, Edmonton, Alberta, Canada*

Abstract

Pregnancy during adolescence increases the risk of adverse pregnancy outcome, especially small-for-gestational-age (SGA) birth, which has been linked to micronutrient deficiencies. Smoking has been shown to be related to lower micronutrient concentrations. Different ethnicities have not been examined. We used a subset from a prospective observational study, the About Teenage Eating study consisting of 126 pregnant adolescents (14–18-year-olds) between 28 and 32 weeks gestation. Micronutrient status was assessed by inductively coupled mass spectrometry. Smoking was assessed by self-report and plasma cotinine, and SGA was defined as infants born <10th corrected birthweight centile. The main outcome measures were as follows: (1) maternal plasma selenium, copper and zinc concentrations in adolescent mothers giving birth to SGA vs. appropriate-for-gestational-age (AGA) infants; and (2) comparison of micronutrient concentrations between women of different ethnicities and smoking habits. The plasma selenium {mean ± standard deviation (SD) [95% confidence interval (CI)]} concentration was lower in the SGA [$n = 19$: 49.4 ± 7.3 (CI: 45.9, 52.9) $\mu g\ L^{-1}$] compared with the AGA [$n = 107$: 65.1 ± 12.5 (CI: 62.7, 67.5) $\mu g\ L^{-1}$; $P < 0.0001$] group. Smoking mothers had a lower selenium concentration compared with non-smokers ($P = 0.01$) and Afro-Caribbean women had higher selenium concentrations compared with White Europeans ($P = 0.02$). Neither copper nor zinc concentrations varied between groups. Low plasma selenium concentration in adolescent mothers could contribute to the risk of delivering an SGA infant, possibly through lowering placental antioxidant defence, thus directly affecting fetal growth. Differences in plasma selenium between ethnicities may relate to variation in nutritional intake, requiring further investigation.

Keywords: micronutrients, small-for-gestational-age, adolescence.

Correspondence: Dr Hiten D. Mistry, Division of Women's Health, King's College London, Women's Health Academic Centre, KHP, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK. E-mail: hiten.mistry@kcl.ac.uk

Introduction

Worldwide, pregnancies during adolescence are associated with a high risk of an adverse obstetric outcome, particularly small-for-gestational-age (SGA) birth delivery (Chen *et al*. 2007). Although teenage pregnancy rates in the United Kingdom have fallen by 3.1% since 2007, they remain among the highest in Western Europe (40.6 births per 1000 women aged 15–17 in 2008 in England and Wales) (Office of National Statistics 2010).

Pregnant adolescents in industrialised countries typically have a poor diet, which may be attributable to their age and socio-economic background (Moran 2007), and nutrient intake in this population has been shown to be inadequate (Crawley 1993). A recent study by our group [the About Teenage Eating (ATE) study] carried out in two inner city populations in the United Kingdom reported a high rate of SGA infants in teenage pregnancies and demonstrated a strong association with reduced folate status (Baker *et al*. 2009). In this study, we have investigated the status of

three essential antioxidant micronutrients previously associated with poor pregnancy outcome: selenium, copper and zinc (Mistry & Williams 2011).

Selenium, an essential trace element, is a cofactor for several important enzymes that play a focal role in antioxidant defence including the glutathione peroxidases (GPxs), which metabolise the products of attack by hydrogen peroxidases and oxidised lipoproteins (Rayman 2000). Selenium has also both structural and enzymatic roles and functions as a catalyst for the production of thyroid hormones (Beckett & Arthur 2005). In a recent study, we reported that selenium concentrations were low in women of reproductive age in the United Kingdom, falling further during pregnancy and this correlated with low plasma and placental GPx activities (Mistry *et al*. 2008). Selenium deficiency has also been linked to several reproductive complications, including SGA infants (Strambi *et al*. 2004; Klapec *et al*. 2008; Mariath *et al*. 2011; Mistry *et al*. 2012). It has also been reported that blood selenium concentrations are lower in tobacco smokers (Northrop-Clewes & Thurnham 2007).

Copper is an essential cofactor for a number of enzymes involved in metabolic reactions; angiogenesis; oxygen transport and antioxidant protection, including catalase; and copper/zinc superoxide dismutase (Cu/Zn SOD) (Gambling *et al*. 2008). During pregnancy, plasma copper concentrations significantly increase, returning to normal non-pregnant values after delivery, which could be partly related to the synthesis of ceruloplasmin, a major copper-binding protein, that in itself is influenced by altered levels of oestrogen (Izquierdo Alvarez *et al*. 2007). Lower copper concentrations have been reported in placentae of SGA pregnancies (Zadrozna *et al*. 2009), but there are limited data regarding maternal plasma copper concentrations in relation to SGA pregnancies.

Zinc is an essential constituent of over 200 metalloenzymes and participates in carbohydrate and protein metabolism, nucleic acid synthesis and antioxidant functions (through Cu/Zn SOD) (Izquierdo Alvarez *et al*. 2007). It has been estimated that the total amount of zinc retained during pregnancy is ~100 mg (Swanson & King 1987). The requirement for zinc during the third trimester is approximately twice as high as that in non-pregnant women (WHO/FAO/IAEA 1996). Plasma zinc concentrations decline as pregnancy progresses and then paradoxically increase towards delivery (Izquierdo Alvarez *et al*. 2007). Zinc supplementation during pregnancy has been reported to significantly increase birthweight and head circumference (Goldenberg *et al*. 1995), highlighting the importance of adequate zinc supply during pregnancy.

Failure to achieve genetic growth potential is a major cause of perinatal morbidity and mortality and is estimated to occur in 10% of pregnancies in the developing countries and up to 25% in nondeveloped countries (Steer 2005). These complications are increasingly evident at lower birthweight centiles. The mechanisms are still to be elucidated but a likely common aetiological factor for SGA is placental ischaemia/hypoxia (Biri *et al*. 2007), which would be associated with oxidative stress. There are few studies of selenium concentrations in SGA/fetal growth-restricted births (Klapec *et al*. 2008; Llanos & Ronco 2009) and none specifically addressing adolescent pregnancies; there is a similar lack of information about copper and zinc. There are known differences in the UK nutritional intakes between ethnicities (Vyas *et al*. 2003; Donin *et al*. 2010), particularly in a

Key messages

- Maternal selenium concentrations are significantly lower in adolescent pregnant women delivering SGA infants compared with those delivering AGA infants.
- Further research is needed to accurately quantify the levels of micronutrients in adolescent pregnancies and how levels vary over the course of pregnancy.
- The actions of antioxidant micronutrient activities on maternal, fetal and placental health during adolescence need to be elucidated further.

pregnant population from South London (Rees *et al*. 2005); thus, additional variations in these specific micronutrients may also be present. A reduced micronutrient concentration may lead to inadequate antioxidant protection culminating in poor fetal growth. Ischaemia-reperfusion injury may contribute to the oxidative stress and could result in the release of reactive oxygen species into the maternal circulation, possibly resulting in oxidative DNA damage which may underlie development of SGA (Takagi *et al*. 2004).

We hypothesised that the micronutrient concentrations would be reduced in mothers who delivered SGA infants. Because of the potential differences in nutritional intakes, we further hypothesised that differences in micronutrient concentrations would be observed between White European and Afro-Caribbean adolescent pregnant women. As it is well-documented that smoking has a detrimental effect on fetal growth (Kho *et al*. 2009), associations with micronutrient concentrations and smoking habits in the pregnant adolescents were also explored.

The aim of this study, therefore, was to establish the maternal plasma selenium, zinc and copper in adolescent mothers delivering SGA and AGA infants and use these data to investigate any differences in these antioxidant micronutrients between ethnicities and smoking status.

Methods

Subjects

The 126 women contributing to the present study represent a subgroup of the larger ATE study of 500 adolescents from whom samples of adequate volume were available (Baker *et al*. 2009). The study was approved by the Central Manchester Local Research Ethics Committee (local registration no. 03/CM/032) and informed written consent was obtained from all participants; adolescent (14–18-year-olds) singleton pregnancies were assessed for capacity to provide informed consent according to the accepted UK criteria (Gillick v West Norfolk & Wisbech 1985). In order to minimise potential confounding effects of different socio-economic background and lifestyle between Manchester and London, we studied only those 126 pregnant adolescent women recruited to the ATE study between 2004 and 2007 at two hospitals in South London, UK. Exclusion criteria were inability to provide informed consent, pre-eclampsia in previous pregnancy, clotting disorders, HIV/AIDS, haemoglobinopathies, known pre-existing diabetes, renal disease, hypertension, multiple pregnancies or a history of ≥1 previous miscarriage. SGA was defined as individualised birthweight ratio below the 10th percentile (American College of Obstetricians and Gynecologists 2000) and calculated using the customised birthweight centiles (Gardosi & Francis 2006). In addition, birthweight *z*-scores were calculated-corrected for gestational age at delivery from the UK WHO 2006 growth charts (Cole *et al*. 2011).

Sample collection and laboratory methods

A 30 mL, non-fasting sample of venous blood was collected in the early third trimester [mean ± standard deviation (SD): 30.3 ± 2.1 weeks gestation] into chilled collection tubes, containing heparin. The time point that blood was collected coincided with routine clinical blood sampling to maximise compliance. Blood samples were transported on ice to the laboratory and centrifuged at 4°C within 30 min of collection. Plasma was stored at –80°C until analysis.

Plasma concentrations of copper, zinc and selenium were assayed by inductively coupled plasma mass spectrometry (ICP-MS) at *m*/*z* 65, 66 and 78, respectively. Samples and standards (SPEX Certiprep Inc., Metuchen, NJ, USA) were prepared identically in a diluent containing 0.1% 'Triton X-100' non-ionic surfactant (+'antifoam-B'; Sigma, Dorset, UK), 2% methanol and 1% HNO_3 (trace analysis grade), including the internal ICP-MS standards iridium (5 μg L^{-1}), rhodium (10 μg L^{-1}), gallium (25 μg L^{-1}) and scandium (50 μg L^{-1}). For all three analytes, the ICP-MS was run in 'collision-reaction cell mode', with pure H_2 as the cell gas to maximise sensitivity for ^{78}Se determination. Aspiration was through a single sample line via a Burgener-Miramist PEEK nebuliser (Burgener-Miramist Inc., Mississauga, ON, Canada). Calibrations for all micronutrients were in the range of 0–50 μg L^{-1}. The quality of analysis was assured using appropriate reference materials (Seronorm and

Table 1. Demographic, obstetric and pregnancy data of subject groups used in the study

Parameter	AGA ($n = 107$)	SGA ($n = 19$)
Age (years) (mean ± SD)	17.5 ± 0.7	17.6 ± 0.8
Ethnic group [*n* (%)]		
White European	61 (57)	5 (26)
Afro-Caribbean	46 (43)	14 (74)
Booking body mass index (kg m^{-2}) (mean ± SD)	24.2 ± 5.2	25.6 ± 5.5
Smoking status [*n* (%)]		
Non-smoker	77 (72)	12 (63)
Smoker	30 (28)	7 (37)
Parity [*n* (%)]		
Nulliparous	102 (95)	19 (100)
Multiparous	5 (5)	0 (0)
Gestational age at delivery (weeks) (mean ± SD)	39.8 ± 1.7	38.9 ± 2.7
Mean birthweight (g) (mean ± SD)	3344 ± 521	2399 ± 456
Corrected birthweight centile [median (IQR)]	47.1 (27, 68.2)	0.2 (0.6, 8.4)
Preterm [*n* (%)]	10 (9)	2 (11)
Caesarean section [*n* (%)]	19 (18)	5 (26)
Selenium ($\mu g\ L^{-1}$) [mean (95% CI)]	65.1 (62.7, 67.5)	49.4 (45.9, 52.9)*
Zinc ($\mu g\ L^{-1}$) [mean (95% CI)]	634.4 (580.5, 688.2)	708.1 (510.4, 905.8)
Copper ($\mu g\ L^{-1}$) [mean (95% CI)]	2059.6 (1991.1, 2128.1)	1960.2 (1712.5, 2207.5)

AGA, appropriate-for-gestational age; CI, confidence interval; SGA, small-for-gestational age; IQR, interquartile range; SD, standard deviation. *$P < 0.0001$. Data were presented as means ± SD or median [IQR] as appropriate, except for preterm births, smoking status, parity, ethnicity and Caesarean sections, which are shown as number (percentage).

UTAK; Nycomed Pharma AS, Zurich, Switzerland). Trace element free techniques were used during collection and analysis, following guidelines from the International Zinc Nutrition Consultative Group. Both intra- and inter-assay coefficients of variances were <5%.

Smoking history was ascertained by direct questioning and verified by plasma cotinine, measured by solid-phase competitive chemiluminescence immunoassay (DPC, Gwynedd, UK). Responses were coded as smokers or non-smokers, which included ex-smokers.

Statistical analysis

All tests were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Data were tested for normality of distribution using the Kolmogorov–Smirnov test. Summary data are presented as mean ± SD. Between-group comparisons were made using Student's *t*-tests. Multiple logistic regression models for AGA/SGA with selenium, smoking and ethnicity individually and together were also conducted, and partial correlation was used for ethnicity as a possibly confounding factor. Pearson's correlation test was used to test associations. The null hypothesis was rejected where $P < 0.05$.

Results

Subjects

Table 1 describes the demographic, obstetric and pregnancy outcome data of the 126 women for whom blood samples were available. More detailed descriptions have been previously published (Baker *et al.* 2009). The two ethnic groups were well-matched for age and BMI; the subgroup of participants used in this study showed no significant difference in any outcome variable when compared with the remaining study population (Baker *et al.* 2009). By definition, both the bithweights and the customised birthweight centiles were significantly lower in the SGA group (Table 1).

SGA

Nineteen mothers delivered SGA infants and the median-corrected birthweight centiles for all infants

Table 2. The plasma selenium, copper and zinc concentration [mean (95% CI)] in adolescent mothers delivering spilt by ethnicity and smoking habit

	Selenium (μg L^{-1})	Copper (μg L^{-1})	Zinc (μg L^{-1})
White European	60.3 (CI: 58.0, 62.7)	2021.7 (CI: 1931.9, 2111.4)	646.8 (CI: 590.0, 703.5)
Afro-Caribbean	65.9 (CI: 61.7, 70.1)*	2068.3 (CI: 1965.2, 2171.4)	642.3 (CI: 548.7, 735.9)
Non-smoker	64.6 (CI: 61.9, 67.4)	2029.8 (CI: 1952.6, 2107.0)	647.5 (CI: 575.9, 719.2)
Smoker	58.1 (CI: 54.1, 62.0)*	2080.3 (CI: 1937.9, 2222.6)	640.5 (CI: 577.5, 703.6)

CI, confidence interval. *$P < 0.05$ between ethnicity and smoking habit for selenium only.

in this study were below the 50th centile (Table 1). The plasma selenium concentration [mean ± SD (95% CI)] was lower in the mothers who gave birth to SGA infants [49.4 ± 7.3 (CI: 45.9, 52.9) μg L^{-1}] compared with the AGA infants [65.1 ± 12.5 (CI: 62.7, 67.5) $P < 0.0001$; Table 1]. Furthermore, a significant positive association was observed between selenium concentrations and birthweight z-scores (r = 0.203, $P = 0.03$; partial correlation = 0.29; $P = 0.002$, after adjustment for ethnicity). No differences were observed between groups for copper or zinc ($P > 0.05$ for both; Table 1).

Smoking

Serum selenium showed that smokers (verified by plasma cotinine) had lower plasma selenium concentrations ($n = 89$) compared with non-smokers ($n = 37$, $P = 0.01$; Table 2). No significant differences were observed for copper or zinc ($P > 0.05$).

Ethnicity

Plasma micronutrient concentrations were compared between White European ($n = 66$) and Afro-Caribbean ($n = 60$) mothers. The selenium concentration was lower in White European compared with Afro-Caribbean women ($P = 0.02$; Table 2). No differences were found in the copper or zinc concentration ($P > 0.05$; Table 2).

Multiple logistic regression models indicated selenium as a strong influencing factor and the addition of ethnicity strengthened this; however, smoking and ethnicity individually had no effect (Table 3).

Table 3. Multiple logistic regression analysis of appropriate-for-gestational-age/small-for-gestational-age with covariate selenium and factors ethnicity and smoking, both unadjusted and adjusted odds ratios (OR)

Factor/Covariate	Unadjusted [OR (95% CI)]	Adjusted [OR (95% CI)]
Selenium (μg L^{-1})	1.15 (1.07, 1.23)**	1.16 (1.08, 1.24)**
Ethnicity	7.43 (1.67, 33.16)*	2.15 (0.93, 5.00)
Smoking	2.07 (0.43, 9.90)	1.43 (0.59, 3.43)

CI, confidence interval. *$P < 0.05$; **$P < 0.0001$.

Discussion

This study reports lower plasma selenium concentration, but not copper or zinc in adolescent mothers delivering SGA infants. Selenium deficiency has been associated with obstetric complications, including pre-eclampsia (Mistry *et al*. 2008), preterm birth (Dobrzynski *et al*. 1998) and delivery of SGA infants (Klapec *et al*. 2008). Small size at birth has been postulated to increase the risks of cardiovascular disease in later life and these obstetric complications are increased in adolescent pregnancies (Chen *et al*. 2007), further highlighting the need to investigate this important population.

This study is the first to present data linking reduced maternal plasma selenium with SGA births in adolescent pregnancies from the United Kingdom. We have previously shown that selenium concentrations fall during pregnancy, indicating an increased requirement for selenium in pregnancy as a result of the demands from the growing fetus (Mistry *et al*. 2008) and possibly altered intestinal re-absorption or renal handling (Szybinski *et al*. 2010). This reduced selenium concentration might adversely affect the functional activities of the antioxidant selenoproteins as we have shown previously (Mistry *et al*. 2010), compromising protection against placental oxidative stress, thus detrimentally impacting on fetal growth, although placental selenium concentrations are not

known. The calculated plasma selenium concentration required for maximal plasma GPx activity in non-pregnant adult humans has been estimated to be ~90 μg L^{-1} (Duffield *et al*. 1999), considerably higher than the concentrations observed in the teenage mothers of this study, especially those delivering SGA infants. One factor that could contribute to the lower selenium concentration is the decline in selenium content of flour in the United Kingdom, as the European Union reduced imports of wheat from the United States and Canada, where selenium content of the soil is higher (Jackson *et al*. 2004). A limitation of this study is that baseline, pre-pregnancy selenium concentrations were not available, thus we were not able to ascertain if the adolescents that went on to deliver an SGA infant started with lower selenium concentrations compared with those delivering AGA infants.

Recent reports from Europe and the United States have suggested that blood selenium concentrations are lowered in tobacco smokers (Galan *et al*. 2005; Northrop-Clewes & Thurnham 2007). Smoking is associated with decreased food intake (Osler 1998; Wilson *et al*. 2005), which could itself result in decreased selenium status. Furthermore, tobacco smoking causes inflammation and induces oxidative stress, and the lower selenium concentration may contribute to these factors (Galan *et al*. 2005; Northrop-Clewes & Thurnham 2007; Ellingsen *et al*. 2009). Another possibility is that the increased exposure of smokers to the heavy metal cadmium might decrease the bioavailability of selenium (Galan *et al*. 2005; Northrop-Clewes & Thurnham 2007).

In this adolescent pregnant cohort, a combination of poor eating habits and tobacco smoking may have amplified any reduction in the plasma selenium concentration (Baker *et al*. 2009). This is further substantiated by the finding of Galan *et al*. that women of younger age had a low mean selenium concentration, which were further influenced by nutrient intakes and smoking (Galan *et al*. 2005). We anticipated that because of the characteristic poor diet in this population (Baker *et al*. 2009), the copper, selenium and zinc concentrations would be lower than older mothers; however, our data do not support this as similar levels were found to that previously reported in slightly older White European primigravidae (Mistry *et al*. 2008); this may reflect the general decline in selenium intake in this population from the United Kingdom. Future prospective studies of age-related profile of selenium concentrations, including adolescents and older mothers, would be of interest in this regard.

The differences in selenium concentrations between different ethnicities may be related to the nutritional intakes in women from different cultural backgrounds (Kant & Graubard 2007). Studies of selenium concentrations relating to ethnic differences in a UK cohort have yet to be completed.

A further limitation of this study is a large proportion of the women for whom samples were available, were 17–18 years in age; future follow-up work is required focussing on the more vulnerable younger adolescents (12–16 years). Also, the numbers in this study were small and, thus, future studies with larger sample sizes and a wider spread of ethnicities and measurements of the respective micronutrient antioxidant activities (GPxs and SODs) are required to confirm these initial results. The results of our study highlight the importance of monitoring maternal nutrition, particularly the micronutrient selenium intake and concentrations during adolescent pregnancies. Prenatal guidance needs to be made clear to ensure that women and practioners are aware of the nutritional requirements during pregnancy and how healthy diet can prevent diseases of pregnancy in this venerable high-risk adolescent group. This study provides preliminary evidence on the importance of proper education of good nutrition and the potential need for future selenium supplementation studies.

Acknowledgements

We thank all the adolescents who participated in the study and all the ATE team for their efforts with the collection of samples and data. Special thanks go to Cindy Hutchinson, Dympna Tansinda, Gina Bennett, Gemma Wild and Lorna Carruthers (midwives). Thanks also to Paul Seed (King's College London) for statistical assistance and Simon Wheeler for helping with the database and sample identification.

Source of funding

This study was financially supported by Tommy's Charity as is HDM (Charity no. 3266897). ALB is partly funded by NIHR Biomedical Research, Centre at King's College London/Guy's and St Thomas' Foundation Trust.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

HDM formulated and organised the project, analysed the data and wrote the majority of the manuscript; FBP assisted in the data analysis; SDY and LOK coordinated/ran the selenium assays; ALB assisted with sample identification and transporting samples; LP and PNB were the principal investigators and designed the ATE study.

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