Maternal selenium status during early gestation and risk for preterm birth

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ABSTRACT

Background: Preterm birth occurs in 5%–13% of pregnancies. It is a leading cause of perinatal mortality and morbidity and has adverse long-term consequences for the health of the child. Because of the role selenium plays in attenuating inflammation, and because low concentrations of selenium have been found in women with preeclampsia, we hypothesized that low maternal selenium status during early gestation would increase the risk of preterm birth.

Methods: White Dutch women with a singleton pregnancy (n = 1197) were followed prospectively from 12 weeks' gestation. Women with thyroid disease or type 1 diabetes were excluded. At delivery, 1129 women had complete birth-outcome data. Serum concentrations of selenium were measured during the 12th week of pregnancy. Deliveries were classified as preterm or term, and preterm births were subcategorized as iatrogenic, spontaneous or the result of premature rupture of the membranes.

Results: Of the 60 women (5.3%) who had a preterm birth, 21 had premature rupture of the membranes and 13 had preeclampsia. The serum selenium concentration at 12 weeks' gestation was significantly lower among women who had a preterm birth than among those who delivered at term (mean 0.96 [standard deviation (SD) 0.14] µmol/L v. 1.02 [SD 0.13] µmol/L; t = 2.9, p = 0.001). Women were grouped by quartile of serum selenium concentration at 12 weeks' gestation. The number of women who had a preterm birth significantly differed by quartile (χ^2 = 8.01, 3 degrees of freedom], p < 0.05). Women in the lowest quartile of serum selenium had twice the risk of preterm birth as women in the upper three quartiles, even after adjustment for the occurrence of preeclampsia (adjusted odds ratio 2.18, 95% confidence interval 1.25–3.77).

Interpretation: Having low serum selenium at the end of the first trimester was related to preterm birth and was independent of the mother having preeclampsia. Low maternal selenium status during early gestation may increase the risk of preterm premature rupture of the membranes, which is a major cause of preterm birth.

Preterm birth occurs in 5%–13% of pregnancies and is a major public health concern worldwide.[1] Preterm birth, defined as delivery before 37 weeks' gestation, is the leading cause of perinatal mortality and morbidity.[2] Short- and long-term consequences to the health of the child include cerebral palsy, respiratory distress syndrome, neurodevelopmental impairment, learning difficulties and behavioural problems.[2] Despite substantial efforts to explain the mechanisms involved, the incidence of preterm birth is on the rise. For example, in the United States, the incidence increased from 9.5% in 1981 to 12.7% in 2005.[1] Consequently, it is important to identify factors that may contribute to preterm birth, particularly those factors that are preventable.

Maternal risk factors for preterm birth include a previous preterm delivery, black race, low socioeconomic status, poor nutrition or becoming pregnant soon after a previous delivery.[1] Risk factors for preterm birth during gestation include multiple-gestation pregnancy and an intrauterine infection that triggers an inflammatory response.[1,3] Endocrine conditions such as diabetes and dysfunction of the thyroid have also been associated with preterm birth, sometimes linked to preterm premature rupture of the membranes.[4,5]

The trace mineral selenium, available from food (though to a greater or lesser extent according to region), can interact with a number of these risk factors.[6–9] It has been implicated in pregnancy outcome,[9–12] and it plays a role in the immune response and the body's resistance to infection.[6] Enzymes containing the mineral, selenoenzymes, can attenuate the excessive

inflammatory response associated with adverse pregnancy outcomes, downregulating the expression of pro-inflammatory genes.[6–8] A polymorphism in the gene encoding the seleno-protein SEPS1 has been shown to affect the risk of preeclampsia, a condition that has a strong inflammatory component that is an important cause of preterm birth.[8] In addition, low sele-nium status has been identified in women with preeclampsia.[12]

We hypothesized that low maternal selenium status (as measured by low serum selenium con-centration early in gestation would be associated with preterm birth. Previous small studies have compared plasma selenium and plasma/erythrocyte glutathione peroxidase in mothers and their babies during both term and preterm deliveries. Although lower values have often been found in mothers who had their babies preterm than in mothers who had their babies at term, the findings were inconsistent.[13–15] We did a prospective study to assess selenium status in a large cohort of pregnant women who were fol-lowed from early gestation to delivery.

Methods

Participants and samples

The study was done in the city of Eindhoven, the Netherlands. Residents of the Netherlands are known to have relatively low selenium sta-tus.[16] Over a period of two years, we identified 1702 women who could potentially participate in the study. To avoid language barriers and possible confounding by ethnicity, only white Dutch women ($n = 1507$) were included in the study, and 79% of them ($n = 1197$) gave their consent. The nonrespondents did not signifi-cantly differ from the respondents in terms of age, parity or level of education (data not shown). Women with known thyroid disease ($n = 21$) or type 1 diabetes ($n = 5$), women who had become pregnant after hormonal stimulation ($n = 8$) and women with a multiple-gestation pregnancy ($n = 8$) were excluded from the study. A total of 1155 eligible women were fol-lowed throughout their pregnancies.

Blood samples were drawn at 12 weeks' ges-tation. Demographic data (age, income, marital status and level of education), lifestyle character-istics (smoking status, consumption of alcohol and body mass index) and previous obstetric his-tory were recorded. Complete data were missing for 26 women, so data for 1129 women were used in the analysis.

This study was approved by the Medical Ethics Committee of Máxima Medical Centre in Eindhoven–Veldhoven.

Outcomes

Gestational age was assessed by calculating from the date of the last menstrual cycle and from an ultrasound scan during what was presumed to be the 12th week of pregnancy. If a discrepancy of more than seven days was seen between these two measurements, a second ultrasound scan was done within two weeks to reassess gesta-tional age. Preterm birth was defined according to the World Health Organization (WHO) defini-tion (birth before 37 weeks' gestation). Preterm births were subcategorized as follows:[1] iatro-genic, or delivery for maternal or fetal indica-tions (e.g., preeclampsia or intrauterine growth restriction), in which labour was induced or the infant was delivered by prelabour cesarean sec-tion; idiopathic, or spontaneous preterm labor with intact membranes; and preterm premature rupture of the membranes with either a vaginal or a cesarean birth.

Serum concentrations of selenium were mea-sured at 12 weeks' gestation by mass spectrom-etry with inductively coupled plasma using an Elan 6100 Dynamic Reaction Cell Plus (PerkinElmer, Waltham, Massachusetts). The amount of selenium 78 was measured using methane gas (0.5 mL/min) in the dynamic reac-tion cell to remove the argon dimer from the background. Butanol was used to increase the sensitivity of the signal.[17] The within-run coeffi-cient of variation was 2.1%–2.6% and the between-run coefficient of variation was 3.1%–5.6% ($n = 10$). Accuracy was assured by analyz-ing four samples of serum from the Trace Ele-ments External Quality Assessment Scheme (University of Surrey, Guildford, Surrey, UK) and the following certified reference materials: Seronorm Serum JL4409 (Nycomed, Norway), which had a mean concentration of 0.90 (stan-dard deviation [SD] 0.04) µmol/L after five determinations (certified mean 0.92 µmol/L, range 0.84–1.00 µmol/L), and Seronorm Serum NO0371, with a mean concentration of 1.76 (SD 0.04) µmol/L (certified mean 1.72 µmol/L, range 1.61–1.83 µmol/L). The detection limit was < 0.01 µmol/L.

Statistical analysis

The normal distribution of the concentrations of selenium was confirmed with the Kolmogorov–Smirnov test ($Z = 1.13$, $p = 0.16$).

To evaluate whether preterm birth was related to maternal selenium status, we used a *t* test to compare the mean selenium concentrations between the term and preterm groups. When we examined the effect of different cut-offs for sele-nium concentration on the percentage of preterm births, significant effects up to the 25th percentile

could be seen. We therefore divided the women into quartiles according to serum selenium concentration. We did a series of univariable logistic regression analyses with overall preterm birth as the dependent variable and selenium concentration at 12 weeks' gestation as the independent variable. Finally, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for selenium in relation to preterm birth by entering several risk factors into multiple logistic regression analyses. These risk factors included demographic characteristics (age, income, marital status and level of education), life-style factors (smoking status, consumption of alcohol and body mass index) and obstetric history (previous miscarriage, parity and diastolic pressure > 90 mm Hg at 12 weeks).[1,18,19] To investigate the effect of selenium on preterm birth independent of the occurrence of preeclampsia, preeclampsia was entered into the regression model as a covariate.

Results

Of the 1129 women, 60 (5.3%) had preterm births, 50 of which occurred between 33 and 37 weeks' gestation and 10 of which occurred before 33 weeks' gestation.

The demographic and lifestyle characteristics, obstetric histories and birth outcomes of the women who participated in the study are shown in Table 1. Significantly more primiparous than multiparous women had a preterm birth. Moreover, preterm birth occurred significantly more often among women who had preeclampsia. The mean serum selenium concentration was 1.01 (SD 0.13) μmol/L for the group as a whole, 1.02 (SD 0.13) μmol/L for the 1069 women with a term delivery and 0.96 (SD 0.14) μmol/L for the 60 women with a preterm delivery (two-tailed $t = 2.9$, $p = 0.003$). Women were grouped into quartiles using serum selenium concentration at 12 weeks' gestation: quartile 1 < 0.92 μmol/L ($n = 288$); quartile 2 = 0.92–1.01 μmol/L ($n = 280$); quartile 3 = 1.02–1.10 μmol/L ($n = 283$); and quartile 4 > 1.10 μmol/L ($n = 278$). The proportion of women who delivered prematurely differed significantly by quartile, with corresponding percentages of 8.3%, 5.4%, 3.8% and 3.5% ($\chi^2 = 8.0$, 3 degrees of freedom [df], $p = 0.04$).

Table 2 shows the different subcategories of preterm birth with the corresponding mean gestational age at delivery and the mean selenium concentration at 12 weeks' gestation. Preterm premature rupture of the membranes was the largest subcategory and accounted for 35% of the preterm births. There were 24 preterm births (8.3%) among the 288 women in the lowest quartile of serum selenium. There were 36 preterm

Table 1: Characteristics of the 1129 pregnant women for whom complete data on birth outcomes were available

Characteristic	Birth outcome, no. (%) of women*		
	Term $n = 1069$	Preterm $n = 60$	p value
Age, yr, mean (SD)	30.5 (3.6)	29.9 (3.1)	0.160†
Primiparous	491 (46)	43 (72)	
Multiparous	578 (54)	17 (28)	< 0.001‡
1 child	456 (43)	12 (20)	0.410‡
2 children	109 (10)	2 (3)	0.460‡
≥ 3 children	13 (1)	3 (5)	0.009‡
With a partner	1048 (98)	57 (96)	
Single	21 (2)	3 (4)	0.110‡
Level of education			
Low	84 (8)	7 (12)	0.290‡
Middle	608 (57)	37 (62)	0.470‡
College or pre-university	299 (28)	12 (20)	0.180‡
University	78 (7)	4 (7)	0.850‡
Monthly income, US$			
< 1500	63 (6)	7 (12)	0.770‡
1500–2000	142 (13)	11 (18)	0.260‡
2000–3000	546 (51)	28 (47)	0.500‡
> 3000	318 (30)	14 (23)	0.290‡
Smoking habit			
Never	590 (55)	33 (55)	0.790‡
Stopped earlier in life	257 (24)	11 (18)	0.310‡
Stopped before pregnancy	94 (9)	7 (12)	0.450‡
< 10 cigarettes/d	109 (10)	7 (12)	0.830‡
10–20 cigarettes/d	19 (2)	2 (3)	0.380‡
Consumption of alcohol			
Never	342 (32)	21 (35)	0.660‡
Stopped before pregnancy	588 (55)	35 (59)	0.590‡
≤ 2 units/wk	107 (10)	2 (3)	0.110‡
> 2 units/wk	32 (3)	2 (3)	0.880‡
Obstetric features			
Previous miscarriage	190 (18)	13 (22)	0.440‡
Diastolic BP at 12 wk, mm Hg, mean (SD)	69 (8.7)	69 (8.1)	0.980†
Diastolic BP at 24 wk, mm Hg, mean (SD)	66 (7.7)	67 (7.3)	0.990†
No. with diastolic BP > 90 mm Hg			
at 12 wk	19 (2)	1 (2)	0.950‡
at 24 wk	7 (1)	1 (2)	0.360‡
No. of women referred because of preeclampsia	60 (6)	13 (22)	< 0.001‡
Gestational age at delivery, wk, mean (range)	39.6 (37.0–42.6)	34.6 (26.1–36.6)	< 0.001†
Birth weight, g, mean (SD)	3523 (485)	2469 (624)	< 0.001†
Placental weight, g, mean (SD)	622 (128)	567 (152)	0.034†
Serum selenium at 12 wk, μmol/L, mean (SD)	1.02 (0.13)	0.96 (0.14)	0.003†

Note: BP = blood pressure, SD = standard deviation.
*Unless otherwise stated.
† t test.
‡ χ^2 test.

births among the 841 women (4.3%) in the upper three quartiles of serum selenium ($\chi^2 = 7.0$, 1 df, $p = 0.008$).

The results of several single logistic regression analyses that related overall risk of preterm birth to selenium status showed that women in the lowest quartile of serum selenium at 12 weeks' gestation had twice the risk of preterm birth as the women in the higher quartiles (OR 2.0, 95% CI 1.19–3.47).

In the multivariable logistic regression analysis, a low serum selenium concentration was independently related to preterm birth (OR 2.18, 95% CI 1.25–3.77), as were primiparity (OR 2.99, 95% CI 1.59–5.62) and preeclampsia (OR 3.19, 95% CI 1.47–6.91) (Table 3).

Interpretation

The overall incidence of preterm birth in our study (5.3%) is consistent with the rates reported in the literature.[1] Of the demographic, obstetric and lifestyle characteristics that have been previously associated with increased odds of preterm birth,[1,18,19] only primiparity showed a significant association in our study. Because only a few women in our study smoked or consumed more than two units of alcohol each week, it is not surprising that these factors were not significant in our analysis. Body mass index was not significantly related to preterm birth. This may have been because the women in our sample had a relatively favourable mean body mass index of 25 (SD 4.7) kg/m^{2}. Other independent factors that have previously been associated with preterm birth, such as non-white race, type 1 diabetes and multiple-gestation pregnancy, were exclusion criteria in our study.

In addition to primiparity, having preeclampsia and being in the lowest quartile of selenium concentration at 12 weeks' gestation were significantly associated with increased odds of preterm birth.

Although previous studies have linked low concentrations of selenium and the selenoproteins, glutathione peroxidase and thioredoxin reductase, in the plasma and placenta to gestational hypertension or preeclampsia,[12,20–23] both of which are conditions associated with preterm birth,[1] we found that selenium status during early gestation in healthy pregnant women was related to preterm birth and that this association was independent of the mother having preeclampsia.

Previous studies have shown that the Dutch population is marginally deficient in selenium.[16] Comparably low concentrations are also found in the United Kingdom.[12] The reported daily intake of selenium in the Netherlands (58.7 μg) is probably inadequate for the synthesis of selenoprotein P,[16] the carrier of selenium in the plasma.[24]

Selenium (likely in the form of selenoproteins or selenoenzymes) is involved in several pathways that have been implicated in preterm birth, in preterm premature rupture of the membranes and in preeclampsia. These pathways include the body's response to infection, the inflammatory response, placentation, placental ischemia–reperfusion, oxidative stress, the generation of antithyroid antibodies and premature degradation of the extracellular matrix of fetal membranes.[1,3,5,25]

Selenium is required for the body's immune response,[6] so low concentrations in either the mother or the fetus can increase the risk of infection, a major cause of preterm birth.[1] Inflamma-

Table 2: Mean serum selenium concentration at 12 weeks' gestation and mean gestational age at delivery in 60 preterm births categorized by cause

Cause of preterm birth	No. (%) of births	Gestational age at delivery, wk, mean (SD; range)	Serum selenium concentration, μmol/L, mean (SD)
PPROM	21 (35)	35.6 (1.2; 31.2–36.6)	0.94 (0.13)
Iatrogenic			
Preeclampsia	13 (22)	34.1 (1.8; 32.6–36.6)	0.93 (0.12)
Pregnancy-induced hypertension	2 (3)	36.2 (0.2; 36.1–36.4)	0.88 (0.07)
Miscellaneous	8 (13)	34.6 (1.2; 32.5–36.6)	0.98 (0.09)
Idiopathic (spontaneous)			
Preterm uterine contractions	13 (22)	32.6 (3.3; 26.1–36.6)	1.00 (0.11)
Antepartum hemorrhage	3 (5)	35.6 (0.8; 35.1–36.5)	1.06 (0.11)

Note: PPROM = preterm premature rupture of the membranes, SD = standard deviation.

tion may be an underlying factor in many of the pathways implicated in preterm birth. Genetic polymorphisms that lead to an increase in the magnitude or duration of the inflammatory response have been associated with an increased risk of preterm birth, whereas those that lead to a decrease in the inflammatory response have been associated with lower risk.[26] Previous studies have described the various roles that selenium plays in attenuating the excessive inflammatory response associated with adverse pregnancy outcomes.[7,8,27–32]

The selenoprotein, thioredoxin reductase, contributes to the upregulation of heme oxygenase-1 during inflammation and periods of oxidative stress.[33–36] Heme oxygenase-1 and its products (carbon monoxide, biliverdin and ferrous ions [Fe^{2+}]) are vitally important for successful placentation, maintenance of uterine quiescence, regulation of hemodynamic control within the uterus and placenta, protection against ischemia–reperfusion injury, protection against preeclampsia, regulation of the apoptotic and inflammatory cascades in trophoblast cells and for increased vasodilatory (carbon monoxide), anti-inflammatory (bilirubin and carbon monoxide), and antioxidant (biliverdin and bilirubin) effects.[37–39]

In addition, selenoenzymes, such as the glutathione peroxidases, are able to reduce the oxidative stress resulting both from the underdevelopment of the uteroplacental circulation and from placental ischemia–reperfusion by converting lipid hydroperoxides to harmless alcohols while selenoprotein P scavenges peroxynitrite.[31] Selenium species have also been shown to decrease the ratio of matrix metalloproteinases to tissue inhibitors of the matrix metalloproteinases.[40] This ability may potentially reduce the risk of fetal membrane rupture, which is one of the features associated with preterm birth.[25]

Limitations

The strengths of our study are its prospective design and careful recording of obstetric complications by a single researcher who was blind to the selenium status of the participants. Unfortunately, no data were available on whether the women had cervicovaginal or intrauterine infections during pregnancy, both of which are important determinants of preterm premature rupture of the membranes. The mean term of women with preterm premature rupture of the membranes in our study was relatively long, but infection is generally believed to be an important cause of very preterm birth.[41] Our data are most relevant to women with a relatively low selenium status. Once the serum concentration of selenium surpasses a range of 1.02–1.10 μmol/L,

its effect on the odds of preterm birth appears to be attenuated.

We did not consider other variables such as a previous history of preterm birth or a recent delivery. Had we included those variables, we would have had to do a separate analysis for multiparous women, which would have given us only 17 preterm births and little statistical power.

We were further limited by only having enough funding to measure the selenium concentration at a single point during pregnancy. We were unable to measure plasma concentrations of glutathione peroxidase, selenoprotein P or heme oxygenase for financial reasons. However, several studies have shown that, in healthy pregnant women, plasma concentrations of selenium decrease linearly as pregnancy progresses, so measurement at 12 weeks' gestation is likely to be a good representation of subsequent values.[13] We chose to measure selenium during early gestation to increase our chances of seeing any early involvement of selenium in the cause of preterm birth or another adverse outcome. Measurements at a later stage of pregnancy could be confounded by the adverse outcome itself (e.g., a lack of expansion of plasma volume could show up as a higher selenium concentration).[42]

Although we have shown that preterm birth was significantly associated with low selenium status at 12 weeks' gestation and have postulated credible mechanisms as to the reason for this association, we have not shown that a low selenium status is the cause of preterm birth. The association between selenium and preterm birth may be driven by inflammation. The plasma con-

Table 3: Results of multivariable logistic regression analysis of factors associated with increased risk of preterm birth

Factor	OR (95% CI)
Maternal age (unit change per yr)	1.02 (0.94–1.10)
Income < US$1500/month	2.34 (0.77–4.68)
Marital status = single	2.08 (0.69–7.81)
Low level of education	1.01 (0.49–2.05)
Smoking	1.09 (0.63–2.37)
Consumption of alcohol > 2 units/wk	0.62 (0.24–1.79)
BMI (unit change per kg/m^2)	1.03 (0.97–1.08)
Low selenium level (< 25th percentile at 12 wk gestation)	2.18 (1.25–3.77)
Primiparity	2.99 (1.59–5.62)
Previous miscarriage	1.52 (0.78–2.99)
Diastolic pressure > 90 mm Hg at 12 wk gestation	1.01 (0.97–1.05)
Preeclampsia	3.19 (1.47–6.91)

Note: BMI = body mass index, CI = confidence interval, OR = odds ratio.

centration of selenium decreases in proportion to the magnitude of the inflammatory response, whereas the concentration of selenoprotein P in the plasma declines as inflammatory activity and cytokine production increase.[43] In the presence of inflammation or infection, this phenomenon may occur as early as 12 weeks' gestation in women who will subsequently have difficulties during their pregnancies that could result in preterm birth. A small randomized controlled trial in Iran showed a significant reduction in the incidence of premature rupture of the membranes with supplementation of selenium.[11] Those results suggest that the link between selenium status and preterm birth we have observed in our study may be more than just an association.

Conclusion

This study shows that low serum selenium concentration during early gestation is associated with preterm birth and may be linked to preterm premature rupture of the membranes.

Future studies should include measurement of selenoenzymes and heme oxygenase-1 to help clarify the mechanisms involved in preterm birth. Further research in this area is warranted because there may be implications for prevention and treatment, particularly in areas such as Europe where selenium status is relatively low.

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