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A Multicountry Analysis of Maternal Selenium Status in Pregnancy and Lactation and Infant Birth Outcomes: Findings from the Women First Maternal Preconception Study☆

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A B S T R A C T

Background: Maternal selenium deficiency is hypothesized to contribute to risk of adverse outcomes including low birth weight and prematurity, possibly through its role as an antioxidant and/or in thyroid hormone function.
Objectives: We assessed relationships between maternal selenium concentrations during pregnancy with offspring outcomes including birth measurements, low birth weight (<2500 g), prematurity (<37 wk), and small for gestational age (birth weight <10th percentile for gestational age).
Methods: This was a secondary analysis of the Women First Trial (NCT01883193), a randomized controlled study investigating the effect of small-quantity lipid-based nutrition supplement (sqLNS) with 130 μg selenium on fetal growth. sqLNS was started ≥3 mo prior to conception, around 12 wk of gestation, or not at all in women in Guatemala, India, and Pakistan. At 12 and 34 wk of gestation and 3 mo postpartum, maternal serum selenium was measured by inductively coupled plasma mass spectrometry (n = 145–325 per timepoint per site). We used generalized linear models adjusted for study arm, study site, and markers of inflammation to test for associations between maternal selenium status and offspring outcomes including birth anthropometry.
Results: Mean selenium concentrations decreased over the course of pregnancy and were lowest 3 mo postpartum. Selenium was lowest in Pakistan and did not increase with maternal supplementation. Across all sites, we found no significant associations between maternal selenium at 12 and 34 wk with birth weight- length-, or head circumference-for-age z-scores. There were also no associations with low birth weight, small for gestational age, or prematurity.
Conclusions: Maternal selenium supplementation did not impact serum concentrations, suggesting that supplementation may not overcome the impact of low intake and the high demands of pregnancy and early lactation. Larger studies in high-risk regions are needed to further clarify the relationship between maternal selenium deficiency and infant outcomes.
This trial was registered at clinicaltrials.gov as NCT01883193 (registered 18 June 2013).

Keywords: selenium, preconception, micronutrient supplementation, low birth weight, birth outcomes

Introduction

Selenium is a trace element with several important roles through which it may impact fetal health [1]. Selenium is essential for thyroid hormone function as a component of the deiodinase enzymes that regulate thyroid hormone recycling [2]. Because of its incorporation as selenocysteine in glutathione peroxidase and thioredoxin reductase, selenium also acts to neutralize oxidative stress that is increased in many pregnancy complications [3]. Soil selenium content varies worldwide, impacting population selenium status. Climate change is predicted to cause a decline in soil selenium, which may further burden populations at risk of selenium deficiency [4].

Abbreviations: AGP, alpha-1-acid glycoprotein; CI, confidence interval; CRP, C-reactive protein; LBW, low birth weight; SGA, small for gestational age; sqLNS, small-quantity lipid-based nutritional supplement; SVN, small vulnerable newborn; TSH, thyroid stimulating hormone.

☆ In memoriam of KMH.

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Selenium deficiency during pregnancy is associated with adverse maternal and infant outcomes including gestational diabetes, pre-eclampsia, gestational hypertension, and low birth weight (LBW) (<2500 g) [5–8]. Higher dietary selenium intake has been associated with decreased risk of preterm birth [9] and higher birth weight [10]. In animal models, selenium deficiency during pregnancy is associated with impaired fetal growth [11, 12]. Despite its importance in pregnancy and public health, there is insufficient evidence to date to guide appropriate intake during pregnancy to potentially reduce adverse outcomes and prevent deficiency across populations globally [13,14].

An important outcome of interest is the incidence of LBW, small for gestational age (SGA), or prematurity, collectively referred to as "small vulnerable newborns" (SVN) [15]. LBW can be a result of prematurity or being SGA (birth weight less than the 10th percentile for gestational age), reflecting inadequate intrauterine growth [16]. Together, infants born prematurely, SGA, and/or LBW account for two-thirds of all neonatal deaths worldwide [16]. The term SVN has been proposed to refer to infants born in one of these categories to highlight their common risk of neonatal morbidity and mortality [15]. Multiple interventions have been studied for their ability to decrease incidence of SVN and stillbirth, including multiple micronutrient supplements that show benefit over supplementation with folate and iron alone [17,18]. However, it remains unclear which micronutrients are contributing to improved outcomes.

Prior work in our group demonstrated improved length at birth and through age 2 y in children of women who received a preconception lipid-based multiple micronutrient and protein-energy nutrition supplement [for women with low BMI (in kg/m^2) and/or low gestational weight gain] [19–21]. A potential role of selenium in offspring length is of particular interest as improved linear growth in the first 2 y of life is consistently associated with better neurodevelopmental outcomes [22] including in the Women First Trial [23,24]. This study is a secondary analysis to determine whether maternal selenium concentrations respond to supplementation in the vulnerable populations of the Women First Trial, and whether selenium is associated with pregnancy outcomes including fetal growth and SVN classification.

Methods

Study design and intervention

This study was a secondary analysis of the Women First Trial (NCT01883193, clinicaltrials.gov), an individually randomized controlled trial investigating timing of maternal multiple micronutrient and protein-energy supplementation using a small-quantity lipid-based nutritional supplement (sqLNS, Nutriset) on fetal and childhood growth [19,21]. Composition of the sqLNS has been previously described and includes protein, PUFAs, and >20 micronutrients including 130 μg of selenium as selenium selenite and 250 μg iodine [19]. Both exceed the Institute of Medicine's recommended dietary allowance during pregnancy that is 60 μg for selenium and 200 μg for iodine [25]. Women intending to get pregnant within the next year were recruited from rural areas in Guatemala, Pakistan, Democratic Republic of the Congo, and India. Women in each site were randomly divided into 1 of 3 study arms: sqLNS starting ≥3 mo prior to conception through delivery (Arm 1), sqLNS starting at ~12 wk of gestation (after blood testing) through delivery (Arm 2), or local standard of care without sqLNS (Arm 3). Participants in Arms 1 and 2 were cautioned not to take other micronutrient supplements or fortified food products while taking the trial supplements. A protein-energy supplement (without additional micronutrients) was included for participants in Arms 1 and 2 if BMI was <20 kg/m^2 or gestational weight gain was below Institute of Medicine standards [19]. Supplement 2 was started at the initiation of Supplement 1 or when either of the criteria became evident and was continued until delivery. The trial study protocol underwent IRB approval at the University of Colorado. In addition, ethics committees and local Ministries of Health at each research site granted approval. All study participants gave written informed consent. For CONSORT diagram, see Supplemental Figure 1.

This study focused on a subset of women from Guatemala, India, and Pakistan. We did not include any participants from the Democratic Republic of the Congo because *1*) cold chain for biological specimens could not be ensured and *2*) gestational age was not confirmed by first trimester ultrasound. Socioeconomic status score was derived from the number of indicators available to the household from the following: electricity, improved water source, sanitation, man-made flooring, improved cooking fuels, and household assets. Compliance with supplement(s) use was documented by review of daily calendars completed by the study participants and by collection of empty, partially eaten, and unused intervention sachets. Compliance was calculated as the total number of sachets fully eaten divided by the number of days between starting the supplement and delivery [19].

Infant outcome measures

Gestational age was determined by first trimester ultrasound that was successfully accomplished for ~70% of participants because of constraints of the low resource settings, as described previously [19]. Prematurity was defined as <37 completed weeks at birth. Anthropometric measurements (weight, length, and head circumference) were obtained within the first 48 h of life (Seca 334 electronic scale, Seca North America and Neonatal stadiometer, Ellard Instrumentation, Ltd) by trained study personnel. Birth weight, length, and head circumference z-scores were obtained using INTERGROWTH-21st [26] with or without adjustment for gestational age at birth. LBW was defined as a birth weight <2500 g, regardless of gestational age at birth. SGA was defined as birth weight less than the 10th percentile for gestational age at birth based on INTERGROWTH-21st. Infants were designated as SVN if they were premature, LBW, or SGA, or a combination thereof.

Collection of biological specimens and measurement of biomarkers

The University of Colorado study team provided each study site with metal-free supplies for use during the collection, storage, and analyses of all samples. On-site training was provided specific to avoiding environmental contamination during sample collection and processing. Blood samples were collected at 12 wk of gestation by trained study personnel for women in Arm 1 and prior to initiation of supplementation for participants in Arm 2. Blood samples were collected at 34 wk of gestation and 3 mo postpartum for all 3 study arms, except in India that did not

collect specimens for Arm 3 (control). Women were not fasting at the time of blood draw. Spot urine samples were collected at 12 and 34 wk. Samples were stored at −80°C at each site, then shipped to the University of Colorado on dry ice and returned to −80°C until processing, except for specimens retained in India for measurement of inflammatory markers and thyroid stimulating hormone (TSH) as described below.

Maternal serum Se concentrations were measured for all 3 sample timepoints by inductively coupled plasma mass spectrometry (Agilent Technologies 7700x) as previously described [27]. Helium collision cell technology was utilized to minimize argon-based polyatomic interferences. Deficiency was defined as serum selenium below 50 μg/L. Two markers of inflammation, C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP), were measured as previously described [26]. Briefly, CRP was measured using a sandwich immunoassay with electrochemiluminescent detection (#K151STD, Meso Scale Discovery) at the University of Colorado for serum samples from the Guatemala and Pakistan sites. Serum samples collected in India were analyzed at the KLE Hospital Clinical Lab by immunoturbidimetry (Siemens Dimension). AGP was measured using a sandwich enzyme-linked immunoassay (#DAGP00, R&D Systems, Bio-Techne Corp) for all 3 sites. TSH was measured at 12 and 34 wk by 1-step sandwich (samples from Guatemala and Pakistan) or chemiluminescence assay (samples from India). Urinary iodine concentration was measured by inductively coupled plasma mass spectrometry and urinary creatinine by a colorimetric assay (Creatinine Urinary Colorimetric Assay Kit 500701, Cayman Chemical Company) as previously described [28]. Iodine concentrations were adjusted by dividing by creatinine to adjust for concentration of the urine sample (I/Cr, μg/g) as described [28].

Statistical analysis

All analyses were performed in R (v 4.4.0) or Graph Pad Prism 10.2.3. Distribution of continuous variables was visualized using histograms. Analysis of variance (ANOVA) (for continuous variables) or Fisher's Exact Test (for categorical variables) were used to test participant group differences across study sites. Multiple linear regression models were used to test association of Se concentrations with infant anthropometric measurements, TSH, and adjusted urinary iodine. Logistic regression models were used to test for relationships between maternal selenium concentrations and infant binary outcomes including SVN, LBW, SGA, and prematurity. All models were adjusted for site (random effects) and study arm (fixed effects). We also tested whether adjusting for inflammation (CRP or AGP) or compliance with the study supplement as continuous variables altered findings. Sensitivity analyses were performed that included only study participants in Arms 1 and 2 with compliance of ≥90% and to test whether findings were robust to outliers, defined as 3 times the IQR. Significance was set at nominal P value of <0.05.

Results

Participant characteristics

Data were collected between December 2013 and March 2017. Samples from a total of 898 women were included in this study: 330 from Guatemala, 225 from India, and 343 from Pakistan (Table 1). Of the 898, 331 were from Arm 1 (preconception); 348 were in Arm 2 (after ~12 wk of gestation); and 219 were in Arm 3 (control). The India study site did not collect biological samples in Arm 3.

The 3 sites differed among most participant characteristics, including maternal age, parity and BMI, socioeconomic status score, supplement compliance, gestational age at birth, and delivery mode. There were no differences in infant sex between sites. At birth, gestational-age-adjusted z-scores differed for weight and head circumference but not length, a difference in this subgroup compared with the primary trial outcome [19]. A total of 323 infants (36%) met 1 or more criteria for SVN, with Guatemala having significantly fewer than the other 2 sites (Table 1).

Selenium status by gestation, site, and supplementation

Sample size varied by location and timing: Guatemala (n = 217 at 12 wk, n = 325 at 34 wk, n = 266 at 3 mo postpartum), India (n = 209 at 12 wk, n = 145 at 34 wk; 177 at 3 mo postpartum), and Pakistan (n = 209 at 12 wk, 295 at 34 wk, n = 300 at 3 mo postpartum). Samples were measured in 2 batches. For 12 and 34 wk samples, within day precision was 2.6% and between day precision was 4.2%. At 3 mo postpartum, within day precision was 0.8% and between day precision was 1.7%.

Mean selenium concentrations were highest at 12 wk and trended downward during gestation (Figure 1, Table 2). Serum selenium was lowest at 3 mo postpartum (Table 2, Supplemental Figure 2) with 22 total participants having serum selenium <50 μg/L. Selenium concentrations were lowest in Pakistani women at all timepoints (Table 2, Figure 1 and Supplemental Figure 2).

Compared with those who had not started the intervention supplement, consumption of sqLNS containing 130 μg of selenium initiated ≥3 mo prior to conception (Arm 1) resulted in statistically higher maternal serum selenium concentrations at 12 wk of gestation for all sites combined but no site individually (Table 3, Supplemental Figure 2). At 34 wk, participants in Arm 2 had higher serum selenium compared with Arm 3 (control). In Guatemala, supplementation with selenium was associated with higher maternal serum selenium concentrations, regardless of the timing of supplementation (Table 3). The effect of study arm was sensitive to outliers as removal of outliers completely attenuated the statistical relationship (Supplemental Table 1). Results did not substantially differ after adjusting for maternal inflammation or compliance with the study supplement (Supplemental Table 1). There was no association between study arm and maternal serum selenium concentration at 3 mo postpartum (Table 3 and Supplemental Table 1).

Association of selenium concentrations with infant outcomes

Adjusting for study arm and country, there were no statistical associations between maternal selenium at 12 or 34 wk with infant birth weight, length, or head circumference z-scores (Table 4). Adjustment for inflammation (Supplemental Table 2) or compliance with the study supplement (Supplemental Table 3) did not significantly impact model output. A sensitivity analysis including only participants in Arms 1 and 2 with final

TABLE 1
Subject characteristics across study sites

	Guatemala[1]	India	Pakistan	*P* values			
				Guatemala vs. India	Guatemala vs. Pakistan	India vs. Pakistan	Overall
Total n = 898	330	225	343				
Arm 1 (total n = 331)	108	114	109				
Arm 2 (total n = 348)	114	111	123				
Arm 3 (total n = 219)	108	—	111				
Maternal age at enrollment (y)	24.26 ± 4.42	22.13 ± 3.18	23.81 ± 4.07	<0.0001	0.304	<0.0001	<0.0001
Maternal age at delivery (y)	25.66 ± 4.45	23.41 ± 3.16	24.77 ± 4.09	<0.0001	0.013	0.0003	<0.0001
Parity	1.89 ± 1.15	1.14 ± 0.94	1.66 ± 1.54	<0.0001	0.048	<0.0001	<0.0001
SES score (out of 6)	3.87 ± 1.05	3.68 ± 1.08	2.99 ± 1.52	0.216	<0.0001	<0.0001	<0.0001
BMI at enrollment (kg/m^2)	25.47 ± 4.08	19.87 ± 3.33	19.62 ± 2.85	<0.0001	<0.0001	0.692	<0.0001
Underweight	1 (<0.01%)	94 (41.8%)	126 (36.7%)				
Normal Weight	168 (51.2%)	114 (50.7%)	200 (58.3%)				
Overweight/obese	160 (48.5%)	17 (7.6%)	17 (5.0%)				
Supplement compliance (%)	71.74 ± 17.66	89.50 ± 12.09	85.53 ± 17.86	<0.0001	<0.0001	0.043	<0.0001
Arm 1	75.92 ± 13.50	91.17 ± 6.46	87.01 ± 13.35	<0.0001	<0.0001	0.021	<0.0001
Arm 2	67.75 ± 20.08	87.66 ± 15.94	84.76 ± 21.01	<0.0001	<0.0001	0.500	0.0016
Received supplement 2 (Arm 1 and 2 only)	18 (8.1%)	204 (90.7%)	210 (90.5%)	<0.0001	<0.0001	>0.999	<0.0001
Vaginal delivery, n (%)	225 (68.2%)	154 (68.4%)	306 (89.2%)	0.999	<0.0001	<0.0001	<0.0001
Female infant, n (%)	158 (47.9%)	106 (47.1%)	181 (52.8%)	0.863	0.218	0.199	0.310
Gestational age (wk)	39.01 ± 1.31	38.91 ± 2.79	38.5 ± 1.69	0.822	0.005	0.071	0.005
SVN,[2] n (%)	78 (29.2%)	97 (52.2%)	148 (48.8%)	<0.0001	<0.0001	0.515	<0.0001
Unknown[3]	63 (19.1%)	39 (17.3%)	40 (11.7%)	0.656	0.010	0.063	0.021
LBW,[2] n (%)	36 (11.4%)	40 (21.6%)	94 (37.8%)	0.007	<0.0001	0.039	<0.0001
Unknown[3]	13 (3.9%)	27 (12.0%)	11 (3.2%)	0.0003	0.680	<0.0001	<0.0001
SGA,[2] n (%)	59 (23.0%)	75 (43.9%)	97 (39.4%)	<0.0001	0.003	0.058	<0.0001
Unknown[3]	73 (22.1%)	54 (24.0%)	62 (18.1%)	0.608	0.211	0.090	0.193
Premature delivery,[2] n (%)	16 (6.0%)	20 (11.0%)	44 (15.0%)	0.075	0.0006	0.269	0.002
Unknown[3]	62 (18.8%)	43 (19.1%)	49 (14.3%)	0.999	0.120	0.132	0.197
Birth weight (kg)	2.92 ± 0.36	2.78 ± 0.42	2.75 ± 0.45	0.0004	<0.0001	0.745	<0.0001
Birth weight Z-score	−0.84 ± 0.83	−1.18 ± 1.01	−1.24 ± 1.07	0.0004	<0.0001	0.735	<0.0001
GA-adjusted weight Z-score	−0.68 ± 0.80	−1.13 ± 0.87	−0.93 ± 1.01	<0.0001	0.004	0.056	<0.0001
Birth length (cm)	47.77 ± 1.73	48.10 ± 2.10	47.37 ± 2.35	0.182	0.038	0.0003	<0.0001
Birth length Z-score	−0.95 ± 0.92	−0.75 ± 1.12	−1.15 ± 1.23	0.118	0.580	0.0002	<0.0001
GA-adjusted length z-score	−0.74 ± 0.86	−0.60 ± 0.96	−0.74 ± 1.17	0.361	0.999	0.368	0.320
Birth head circumference (cm)	33.44 ± 1.24	33.19 ± 1.35	32.81 ± 1.41	0.096	<0.0001	0.005	<0.0001
Birth head circumference Z-score	−0.61 ± 1.01	−0.79 ± 1.09	−1.11 ± 1.13	0.143	<0.0001	0.003	<0.0001
GA-adjusted head circumference z-score	−0.24 ± 0.99	−0.54 ± 1.02	−0.56 ± 1.11	0.010	0.001	0.970	0.0006
Weight-for-length Z-score	−0.07 ± 0.96	−0.86 ± 0.85	−0.54 ± 1.19	<0.0001	<0.0001	0.004	<0.0001
GA-adjusted weight-for-length Z-score	−0.85 ± 1.17	−1.68 ± 1.19	−1.20 ± 1.34	<0.0001	0.0035	0.0003	<0.0001

Abbreviations: GA, gestational age; LBW, low birth weight; SES, socioeconomic status; SGA, small for gestational age; SVN, small vulnerable newborn.

[1] Values are shown as mean ± SD or number (%).

[2] Denominator removed participants with missing information for that outcome.

[3] Shown as percent of total participants for that study site.

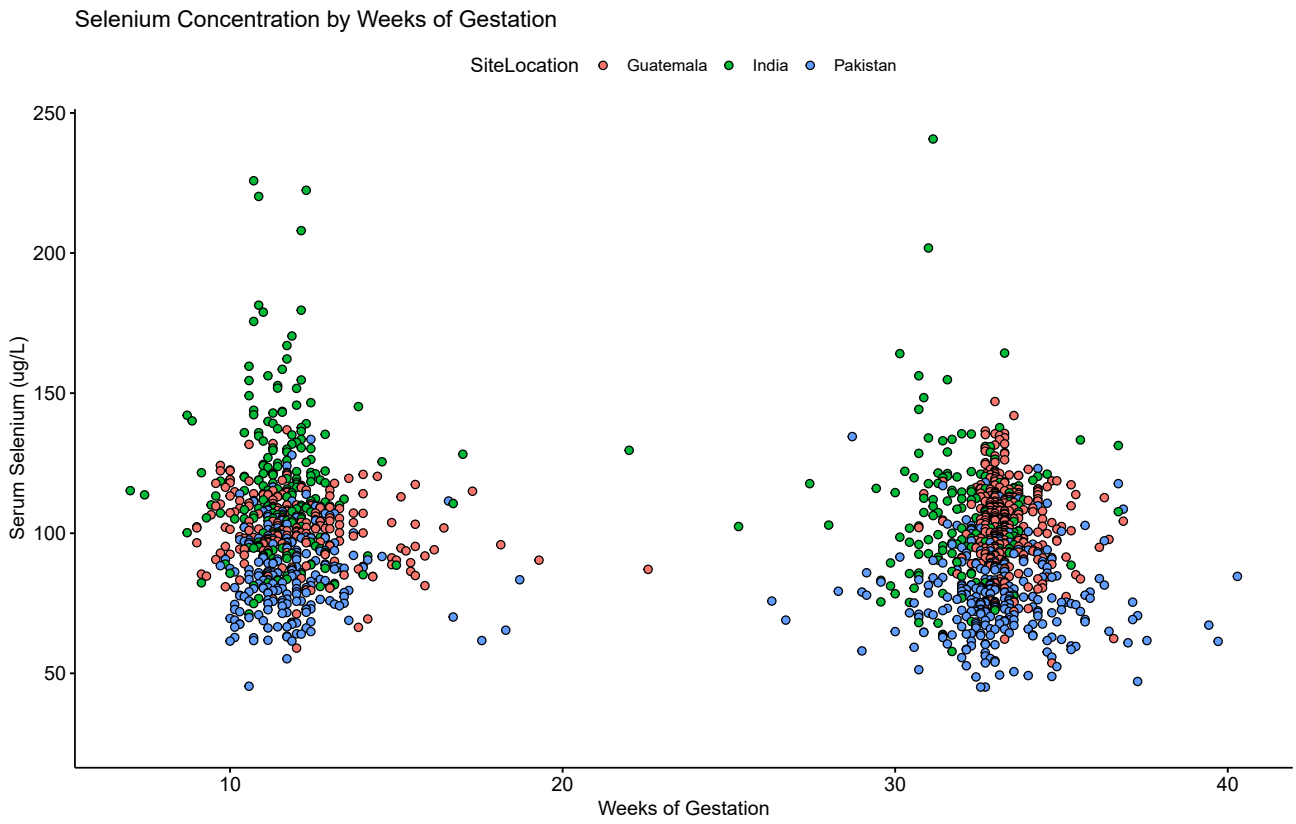

FIGURE 1. Maternal selenium concentration in μg/L by gestational week at the time of collection. Guatemala (red), India (green), Pakistan (blue).

TABLE 2
Mean selenium concentrations (μg/L) at each timepoint, as well as at each study site by study arm

Site		12 wk				34 wk				3 mo postpartum			
		n	Mean	SD	Deficient[1]	*n*	Mean	SD	Deficient	*n*	Mean	SD	Deficient
All	—	635	101.93	23.11	1	765	94.50	21.30	7	743	90.93	22.63	22
Guatemala	Arm 1	104	102.87	11.95	0	107	104.83	14.10	0	82	98.57	18.43	0
	Arm 2	113	101.34	13.23	0	111	106.31	12.38	0	93	102.49	18.60	1
	Arm 3	—	—	—	—	107	100.47	15.52	0	91	99.16	20.28	0
India[2]	Arm 1	109	120.64	29.60	0	82	105.48	20.26	0	96	97.76	20.22	1
	Arm 2	100	115.13	23.58	0	63	109.42	28.22	0	81	96.93	26.40	1
Pakistan	Arm 1	103	86.82	14.39	0	100	75.64	14.59	6	100	80.47	19.87	5
	Arm 2	106	84.64	14.55	1	95	79.10	14.28	1	98	79.36	19.48	5
	Arm 3	—	—	—	—	100	79.02	15.25	0	102	77.09	19.62	9

[1] Deficiency was defined as serum selenium <50 μg/L.
[2] No biologic samples were collected from Arm 3 participants in India.

compliance ≥90% also showed no relationship of maternal selenium with birth measurements (Supplemental Table 3). Similarly, removal of outliers did not impact model output (Supplemental Table 3).

There was no association between SVN status and maternal selenium concentrations at 12 or 34 wk (Table 5). We separately examined each component of SVN: LBW, SGA, and preterm birth. We did not detect any statistically significant associations, including after adjustment for inflammation (Supplemental Table 4).

Relationship between selenium, thyroid stimulating hormone, and iodine concentrations

Serum TSH concentrations and urinary iodine and creatinine concentrations were measured at 12 and 34 wk as previously published [28]. Mean TSH was numerically higher at 34 compared with 12 wk and was lowest in Pakistan (Supplemental Table 5). Similarly, urinary iodine adjusted for creatinine was also numerically lower in Pakistan with minimal apparent difference between the 2 measurement timepoints (Supplemental Table 6).

Urinary iodine and serum selenium, adjusting for study arm, site, and CRP, were not statistically associated at 12 wk [$\beta = -0.003$; 95% confidence interval (CI): −0.01, 0.00, $P = 0.161$] but were weakly associated at 34 wk ($\beta = 0.004$; 95% CI: 0.00, 0.01, $P = 0.029$). There was no association between maternal serum selenium concentrations with maternal TSH at 12 or 34 wk (Supplemental Table 7). In contrast, maternal urinary iodine adjusted for creatinine was positively associated with maternal TSH at 12 wk only after removing outliers.

TABLE 3
Results of linear regression testing the relationship between mean selenium concentrations (μg/L) and study arm

Timepoint	Site	Comparison	Beta coefficient[1]	SE	95% CI	*P* value
12 wk	All sites	Arm 1 vs. 2	3.052	1.510	0.09, 6.02	0.044
	Guatemala	Arm1 vs. 2	1.289	1.728	−2.12, 4.70	0.457
	India	Arm 1 vs. 2	3.524	3.212	−2.81, 9.86	0.274
	Pakistan	Arm 1 vs. 2	2.234	1.929	−1.57, 6.04	0.248
34 wk	All sites	Arm 1 vs. 3	0.432	1.587	−2.68, 3.55	0.785
	All sites	Arm 2 vs. 3	3.278	1.588	0.16, 6.40	0.039
	Guatemala	Arm 1 vs. 3	4.049	1.945	0.22, 7.88	0.038
	Guatemala	Arm 2 vs. 3	5.657	1.918	1.88, 9.43	0.003
	India	Arm 1 vs. 3	−1.872	3.828	−9.44, 5.70	0.626
	Pakistan	Arm 2 vs. 3	−3.417	2.077	−7.50, 0.67	0.101
	Pakistan	Arm 1 vs. 3	0.504	2.089	−3.61, 4.61	0.810
3 mo postpartum	All sites	Arm 1 vs. 3	1.911	2.015	−2.04, 5.87	0.343
	All sites	Arm 2 vs. 3	2.477	1.997	−1.44, 6.40	0.215
	Guatemala	Arm 1 vs. 3	−1.598	2.955	−7.42, 4.22	0.334
	Guatemala	Arm 2 vs. 3	2.717	2.805	−2.81, 8.24	0.589
	India	Arm 1 vs. 3	0.680	3.341	−5.92, 7.28	0.839
	Pakistan	Arm 2 vs. 3	2.989	2.652	−2.23, 8.21	0.261
	Pakistan	Arm 1 vs. 3	1.666	2.679	−3.61, 6.94	0.535

Abbreviation: CI, confidence interval.
[1] Models were adjusted for either country or for cluster within each country for site-specific analyses.

TABLE 4
Results of multiple linear regression testing the relationship between mean selenium concentrations and offspring birth weight, length, and head circumference z-scores

Measurement	Time	Beta[1]	SE	95% CI	*P* value
Birth weight Z-score	12 wk	−0.002	0.002	−0.01, 0.00	0.471
	34 wk	0.000	0.002	0.00, 0.00	0.853
Birth length Z-score	12 wk	0.001	0.002	0.00, 0.01	0.720
	34 wk	0.0002	0.002	0.00, 0.00	0.932
Birth head circumference Z-score	12 wk	0.001	0.003	−0.01, 0.00	0.857
	34 wk	0.000	0.002	0.00, 0.00	0.993

Abbreviation: CI, confidence interval.
[1] Models were adjusted for study arm and study site (country).

TABLE 5
Results of logistic regression testing the relationship between mean selenium concentrations and infant outcomes

Outcome	Time	OR[1]	95% CI	*P* value
Small vulnerable newborn	12 wk	1.006	0.996, 1.016	0.238
	34 wk	1.000	0.991, 1.010	0.989
Low birth weight (<2500 g)	12 wk	1.001	0.989, 1.012	0.891
	34 wk	0.991	0.980, 1.002	0.123
Small for gestational age (birth weight below the 10th percentile for gestational age)	12 wk	1.007	0.996, 1.017	0.203
	34 wk	1.004	0.994, 1.014	0.469
Premature birth (before 37 completed wk)	12 wk	1.004	0.989, 1.084	0.568
	34 wk	0.998	0.982, 1.014	0.813

Abbreviation: CI, confidence interval.
[1] Models were adjusted for study arm and study site (country).

Discussion

Selenium is a micronutrient of rising interest as deficiency has been reported to be associated with adverse health effects, including during pregnancy [8,29–31]. Selenium needs increase during times of acute stress, including pregnancy [32], yet the evidence for selenium supplementation during pregnancy and lactation remains inconclusive [14]. We aimed to test if supplementation with selenium ≥3 mo before conception would favorably impact maternal serum selenium concentrations and whether serum selenium during pregnancy is associated with fetal growth.

Between the 3 study sites, serum selenium concentrations were lowest in Pakistan at all timepoints examined. Pakistan also had the highest number of study participants with selenium deficiency. In settings primarily reliant on locally grown food, soil selenium content influences serum concentrations [33] and may at least partially explain the observed differences [34]. Soil selenium content is predicted to decrease with rising global temperatures [4], which may place women in this part of the world at further risk of deficiency. One previous study examined serum selenium in pregnant Pakistani women with reported concentrations about twice as high as in our study (mean 179 μg/L in the third trimester) [35]. That study was conducted in a region of Pakistan further north than the present one and in an area with significantly more rainfall [36], which increases soil selenium uptake by crops [37].

Despite higher prevalence of selenium deficiency in Pakistani study participants, provision of an sqLNS with 130 μg of selenium, nearly twice the Institute of Medicine recommended daily allowance for pregnancy [25], failed to increase maternal serum selenium or prevent development of deficiency during pregnancy and at 3 mo postpartum. Our findings suggest that populations at high risk of selenium deficiency have higher needs

during pregnancy and may benefit from development of selenium intake recommendations—which may include supplementation or fortification—specific to regions with low selenium soil content. Furthermore, because serum selenium concentrations decline throughout pregnancy [38,39], deficiency cut-offs may need to vary by trimester.

Differences in selenium concentration between study arms were attenuated after removal of outliers and similarly would not be significant after adjusting for multiple testing. The absence of supplementation effects on maternal selenium concentrations is unlikely to be related to poor compliance with the study supplement because compliance exceeded 85% on average and adjustment for individuals' compliance did not influence model outcomes. Work by others showed that the same sqLNS product raised maternal selenium concentrations at 36 wk of gestation in pregnant women in Malawi [40] where soil selenium is also low [33,34]. Serum selenium concentrations (mean 82 μg/L) were comparable with those from Pakistan in our study. In the Malawi study, statistical differences were only present after adjustment for inflammation as measured by CRP and AGP [40]. Adjusting for the same factors in the present cohort did not reveal any statistical associations.

Selenium concentrations were lowest at 3 mo postpartum with the highest number of women with selenium concentrations below 50 μg/L. Human milk selenium concentrations are closely correlated with maternal selenium status, highlighting the importance of selenium sufficiency to ensure adequate intake for exclusively breastfed infants [41,42]. Additional investigations are needed to determine the clinical impact of low maternal serum selenium during lactation on human milk composition and infant growth. Providing 75 μg of selenium to HIV-positive breastfeeding women in Malawi for 6 mo postpartum did not raise serum, breast milk, or infant selenium concentrations [42]. Both our study and theirs used inorganic selenium selenite that has lower bioavailability compared with organic selenium (as selenomethionine). Thus, organic selenium may be more effective at raising maternal serum concentrations and warrants additional consideration for future trials in populations at high risk of selenium deficiency [42,43].

The majority of neonatal deaths worldwide occur in infants classified as SVN [15,16]. Interventions aimed at improving fetal growth and preventing prematurity would have the capacity to reduce neonatal mortality and morbidity and improve long-term human capital [17]. Furthermore, growth in the first 2 y of life is closely related to improved neurodevelopmental outcomes [22], whereas growth beyond age 2 does not appear to be [44]. In this cohort we found no association between maternal selenium concentrations and SVN classification. A study of HIV-infected pregnancy women in Tanzania, which has generally low soil selenium [45], found similarly null results for infant outcomes with 200 μg selenomethionine started during the second trimester [46]. Inability to detect differences may related to the role of other factors not assessed in this secondary study such as zinc [26,47] or iron [48], which are also known to be associated with birth weight and other outcomes. We also did not find a statistical relationship between maternal selenium concentrations and premature birth. The relationship between maternal selenium status and prematurity remains unclear including in areas with low soil selenium. Some cohorts [49–51] and a meta-analysis [52] showed higher risk of prematurity with lower maternal serum selenium concentration, whereas others have found no association [46,53,54]. Finally, we did not observe an association between LBW or SGA and maternal selenium concentrations. A cohort in Norway had similar negative findings to ours [10], whereas a study from China found that women with selenium deficiency (defined as <45 μg/L) were more likely to have infants born SGA or LBW [6]. It is possible that there may be a threshold below which selenium is more closely linked to birth outcomes. Because of the small numbers of study participants with overt deficiency in our cohort, we could not do a similar subgroup analysis.

We found no associations between maternal selenium concentrations and birth weight, length, or head circumference z-scores. Studies of pregnant individuals in Poland [29] and Spain [53] likewise found no statistical associations between maternal serum selenium and birth anthropometric measurements. A meta-analysis also failed to find an association between maternal selenium concentrations and birth weight [47]. This study adds to existing evidence that variability in maternal selenium status may not be associated with fetal growth.

A recent individual participant data meta-analysis found a stronger effect of multiple micronutrient supplements on birthweight if compliance exceeded 90% [55]. We performed a sensitivity analysis limited to participants with ≥90% compliance but detected no statistical relationship between maternal selenium concentrations and birth anthropometric measurements. Our sample size was several orders of magnitude lower (n = 246) than the meta-analysis (n = 61,204) that limited our power.

A possible mechanism for selenium's impact on fetal growth is through its role in thyroid hormone function [2]. Thyroid hormones are essential regulators of intrauterine growth and brain development, with the embryo completely reliant on normal maternal thyroid function in the first trimester [56]. Subclinical hypothyroidism is known to increase risk of SGA and LBW [57]. We did not detect a statistical relationship between maternal TSH concentrations, a marker of thyroid function, and serum selenium at any timepoint. Prior work by others demonstrated a stronger relationship between maternal TSH and selenium concentrations when serum selenium was lower [58]. Future work may need to incorporate assessment of active thyroid hormones such as T3 and T4 to more completely define this relationship. We also tested for a relationship between urinary iodine and selenium [59] but found only a weak statistical relationship at 12 wk.

Although this study has many strengths, it is not without limitations. Not all participants had biospecimens collected that may have introduced some selection bias. We had small numbers of premature infants that limited our power to detect associations between preterm birth and selenium concentrations. The blood samples were not collected while fasting; however, because all women were not fasting, we anticipate that any effects would be randomly distributed and therefore unlikely to influence the overall results. Nonfasting samples have also been used in similar work by others [40]. In addition, serum selenium concentration may not be the most accurate reflection of total body selenium stores. Use of whole blood, nail, or hair samples may have provided more information about long-term selenium status. Alternatively, measurement of glutathione peroxidase activity might be more revealing of function [43].

We did not assess other sources of selenium intake in the participants' diet in part due to limitations of accurate information on regional selenium variations in local crops. Some studies have shown a relationship between pregnancy outcomes and dietary selenium but not selenium status [9]. The mechanisms for this discrepancy are not currently understood and warrant additional investigation. Finally, selenium absorption can be impacted by other dietary components such as heavy metals that were not examined here [43].

In conclusion, our study contributes to the paucity of data on selenium status in pregnancy and lactation. Preconception selenium supplementation as part of a comprehensive lipid-based multiple micronutrient supplement did not increase selenium concentrations or prevent deficiency, particularly during lactation. Maternal selenium concentrations were not associated with fetal growth outcomes at birth nor with maternal thyroid function. Larger trials of selenium status during pregnancy and lactation will be needed in populations at risk of deficiency to more completely assess the clinical impact of low selenium on fetal growth, prematurity, and human milk composition.

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Author contributions

The authors' responsibilities were as follows – NFK, KMH: conceptualization; JLW, JFK: methodology; SPG, JLW, JL, KS: formal analysis; JFK: investigation; SPG, KS: software; SPG, JLW, JFK: data curation; SPG, JLW: writing—original draft preparation; JLW, JFK, KS, NFK: writing—review and editing; SPG: visualization; KS, NFK: supervision; JLW, JFK, NFK, KMH: project administration; NFK, KMH: funding acquisition; SPG, NFK: primary responsibility for final content; and all authors: have read and agreed to the published version of the manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

A deidentified dataset generated during and/or analyzed during this study is available from the corresponding author on reasonable request.

Informed consent statement

Written informed consent was obtained from all participants involved in the study.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Colorado Multiple Institutional Review Board (protocol code 13-2160; approved in 2013). In addition, the protocol was reviewed by the local or/and national ethics committees for each of the 4 sites (registered with United States Office of Human Research Protection and with Federal-wide Assurance in place).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2025.101279.

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