CYPRESS

OUR SCIENCE IS GOLDEN

RESEARCH SUMMARY: MATERNAL HEALTH

Importance of selenium before, during, and after pregnancy

Research Summary

EXECUTIVE SUMMARY

The risk of two important adverse outcomes of pregnancy — Preterm Birth and Preeclampsia — may be selenium responsive. Pregnancy is a dynamic process characterized by an apparent increase in maternal utilization of selenium. Without supplementation, blood levels of selenium progressively decline during pregnancy and lactation. Inadequate selenium status in infants may enhance their vulnerability to adverse health outcomes, including bacterial infection (sepsis), impaired neurological development, and autism.

In this executive summary, evidence supporting the importance of selenium to maternal and infant health is presented from genetic, observational, and interventional studies. Genetic studies — the linking of particular gene variations with particular health outcomes — can provide useful clues to implicating selenium in key mechanistic pathways that contribute to disease. Observational studies test populations of women and infants for associations between selenium status (selenium concentration in blood, hair, or toenails) and risk for particular health outcomes. Finally, interventional studies seek to test whether supplementation with selenium can reduce the risk for adverse health outcomes. Taken together, these are the kinds of scientific evidence that will contribute to the ongoing, deepening understanding of the linkage between selenium, reproductive and infant health. This summary is intended to serve as a starting point for extending dialogue regarding the adequacy of the conventional thinking about the benefits of selenium in a maternal and infant health setting and to provoke the progressive thinking that will inevitably re-shape current practice.

SUMMARY STATEMENTS

- **Low maternal selenium status is associated with an increased risk of preterm birth.**
- **Maternal supplementation with high-selenium yeast has been shown to significantly reduce the risk of spontaneous preterm birth.**
- **Low maternal selenium status is associated with an increased risk of preeclampsia.**
- **Maternal supplementation with high-selenium yeast has been shown to significantly reduce the risk of developing preeclampsia.**
- **Selenium supplementation of preterm infants may reduce the incidence of life-threatening sepsis.**
- **Higher maternal selenium status is associated with improved early neurological development.**
- **Preterm birth and low selenium status in children have been associated with autism.**
- **Adequate selenium intake may be important in ameliorating the toxic effects of heavy metals, such as cadmium, lead, and mercury.**

Selenium and Preterm Birth

Preterm Birth is defined as gestation of less than 37 weeks. Descriptive subclassifications include early (less than 32 weeks) versus late preterm birth, and spontaneous versus non-spontaneous (induced). Spontaneous preterm birth accounts for approximately two-thirds of cases, whereas one-third of preterm births are the result of interventions triggered by concerns for fetal or maternal well-being. The underlying reason for a large percentage of spontaneous preterm births is unexplained. A condition of worldwide importance, preterm birth is recognized as the leading cause of neonatal death[1] (see Appendix for additional information on mechanisms and consequences of preterm birth).

EVIDENCE FROM GENETIC STUDIES

- A search for genetic associations with spontaneous preterm births in 43,000 women of European ancestry points to the potential role of selenium in reducing the risk of preterm birth. The study published in the *New England Journal of Medicine*[2] showed that one of the three gene variants associated with preterm birth was the EEFSEC gene, which encodes for the enzyme that incorporates selenium (in the form of selenocysteine) into all human selenoproteins. This suggests that selenoproteins may mediate key processes that serve as critical regulators of healthy gestational length. It follows that disruption of this regulation through selenium inadequacy may promote preterm birth.

EVIDENCE FROM OBSERVATIONAL STUDIES

- In an analysis of 1129 pregnant Dutch women, study subjects with the lowest serum selenium levels (less than 72.4 micrograms/L) at 12 weeks gestation had more than a two-fold greater risk of subsequent preterm birth than women with higher serum selenium levels (Multivariate Odds Ratio, 95% CI = 2.2, 1.2-3.8).[3]
- It is observed in the African country of Malawi, ranked #1 by the World Health Organization (WHO) as having the highest global risk of preterm birth approaching 20%[4], eighty percent of the population is at risk for selenium inadequacy.[5]

EVIDENCE FROM INTERVENTIONAL STUDIES

- The possibility that maternal selenium supplementation might reduce the risk of preterm birth has been evaluated in a small randomized, double-blind placebo-controlled trial conducted in Iran.[6] Compared to a placebo group, women who received daily supplementation of 100 micrograms selenium-yeast beginning in the first trimester of pregnancy experienced a significant reduction in the risk of preterm premature rupture of membranes (PPROM), a major cause of spontaneous preterm births. Notably, average selenium status of the study participants prior to supplementation was 122 micrograms/L, which is comparable to the average selenium status of women living in North America. An increase in average serum selenium to 169 micrograms/L in the supplemented women was associated with a 2.5-fold reduction in incidence of preterm membrane rupture, compared to the placebo group (p=.01).

Selenium and Preeclampsia

Preeclampsia is a syndrome affecting pregnant women characterized by new onset hypertension and proteinuria. Preeclampsia usually occurs in the last trimester of pregnancy and is a recognized risk factor for preterm birth. The syndrome likely represents a collection of different pathophysiological subtypes, including those cases in which the clinical signs are driven by the maternal response to inadequate placentation (placental preeclampsia) or by an abnormal maternal response to "normal" changes of pregnancy (maternal preeclampsia).[7] The possibility that the most useful predictors and prevention strategies may be subtype-specific is currently being explored and emphasizes the need for personalized approaches.[8]

EVIDENCE FROM GENETIC STUDIES

- In a study comparing preeclamptic women (n=1139) and controls (n=2269), women with preeclampsia were 1.34 times more likely to have a variant of the SELENOS gene, resulting in decreased production of selenoprotein S.[9] The study was prompted by the discovery that this selenoprotein S gene variant is associated with increased levels of circulating inflammatory cytokines, such as TNF-alpha, IL-6, and IL1-beta.[10] An attempt to resolve the genetic factors that drive preeclampsia risk has proven difficult, likely due to the heterogeneity of the syndrome.[11]

EVIDENCE FROM OBSERVATIONAL STUDIES

- Investigators in the UK compared the selenium status of 53 women with preeclampsia to 53 pregnant controls.[12] Women with the lowest toenail selenium levels (mean .49 ppm Se) were more than 4 times more likely to develop preeclampsia (Odds Ratio, 95% CI = 4.4, 1.6-14.9; p=.001). Notably, toenails were collected at the time of preeclampsia diagnosis; these were not pre-diagnostic samples. But toenail selenium levels likely reflect selenium status 3 to 6 months *prior to diagnosis*. Among the women with preeclampsia, 11 women who had preterm birth had significantly lower toenail selenium levels than the 42 women who delivered after 32 weeks (p=.029).
- To investigate the association between selenium status and risk of preeclampsia, data on national incidence of preeclampsia and reported average serum selenium levels in 35 countries were compared.[13] Incidence of preeclampsia was based upon 6,456,570 births, including 222,812 preeclampsia cases. Increasing plasma selenium concentrations was correlated with decreasing preeclampsia incidence (p<.001). The strength of correlation (Pearson r=-.60) indicates that up to 36% of the between-country difference in preeclampsia incidence may be explained by differences in selenium status. This study also provided a comparison of preeclampsia incidence in two countries, Finland and New Zealand, before and after governmental fortification of the population's selenium status in the 1980s. In Finland, incidence of preeclampsia fell 71% from 5.2% prior to fortification to 2.1% after selenium fortification raised average serum selenium levels in adults from 68 micrograms/L to 107 micrograms/L. Similarly, incidence of preeclampsia in New Zealand fell 61% from 6.7% prior to fortification to 1.9% after selenium fortification that was accompanied by an increase in average serum selenium in adults from 68 micrograms/L to 113 micrograms/L.
- An analysis of serum selenium levels at 15 weeks gestation in women from the UK, New Zealand, and Australia enrolled in the Screening for Pregnancy Endpoints (SCOPE) trial showed no significant difference between 244 women with preeclampsia versus 472 unaffected women matched for body mass index (median, 79.0 versus 79.6 micrograms Se/L, respectively).[14]

EVIDENCE FROM INTERVENTIONAL STUDIES

- The possibility that maternal selenium supplementation might reduce the risk of preeclampsia has been evaluated in a small randomized, double-blind placebo-controlled trial conducted in Iran.[15] No cases of preeclampsia developed in 61 women who received daily supplementation with 100 micrograms of selenium-yeast beginning in the first trimester of pregnancy. Preeclampsia developed in 3 of 64 (5%) women in the placebo group. This apparent beneficial effect of selenium supplementation did not reach statistical significance, hampered by low statistical power. The pregnant women in this study receiving supplemental selenium had 18% lower depression scores than their placebo counterparts ($p<.05$).[16]
- In a study in China, daily supplementation of 52 women with 100 micrograms of selenium for 6-8 weeks during late pregnancy was found to prevent the incidence of pregnancy-induced hypertension compared to 48 placebo controls.[17] Gestational edema was also decreased with selenium supplementation.
- In the Selenium in PRegnancy INTervention (SPRINT) study conducted in the UK, 230 pregnant women were randomized to receive 60 micrograms of high-selenium yeast daily from the 1st trimester until term.[18] Selenium supplementation was associated with a significant 70% reduction in the risk of developing preeclampsia and pregnancy-induced hypertension (Multivariate Odds Ratio accounting for compliance, 95% CI = .30, 0.09-1.0 ($p=.049$). Notably, in this study, toenail selenium levels at 16 weeks gestation was the strongest predictor of outcome, even stronger than selenium supplementation. These results raise the intriguing possibility that *periconceptual micronutrient status* (during the first 8 weeks of gestation) may be a more important contributor to preeclampsia risk than micronutrient status at later time periods during pregnancy. This is consistent with data from the Danish National Birth Cohort in which periconceptual multivitamin use (which included selenium, 50 micrograms/day) significantly reduced risk of preeclampsia in normal weight women.[19]

Selenium Supplementation in Preterm Infants: Potential Health Benefits

- Preterm infants have inadequate selenium stores at birth since the accretion of selenium from the mother to the fetus occurs primarily in the 3rd trimester, and the shorter the gestational age, the lower the selenium concentration.[20]
- A recent review of 18 studies showed selenium supplementation of neonates can reduce clinical complications associated with premature births, including reduced hospital stay and costs.[21]
- In a small randomized, double-blind placebo controlled trial in a selenium deficient region of India, selenium supplementation at a dose of 10 micrograms per day given to very low birth weight preterm infants (<1500g or 3.3lbs) completely eliminated culture proven late-onset sepsis (0/45 vs. 6/45, $p=.033$), while also significantly reducing probable sepsis by 56% (i.e., 15.6% vs. 35.6% in control group; $p=.02$).[22] All-cause mortality at 4 weeks was similar in selenium supplemented and placebo groups, 4.4% and 6.7% respectively ($p=.65$).
- In addition, selenium yeast has been shown to be an effective form of selenium for enteral supplementation of preterm infants, as 5 micrograms selenium per day from selenium-yeast increased serum selenium levels from 36 to 44 micrograms/L during the first 14 days postpartum, while serum selenium levels declined in the non-supplemented group from 34 to 26 micrograms/L.[23]

Higher Maternal Selenium Status is Associated with Improved Neurological Development in Offspring

- **Maternal serum selenium levels are inversely associated with neural tube defects**
    - Pregnant women giving birth to babies with neural tube defects had significantly lower serum selenium levels compared to those giving birth to healthy babies (median 42 micrograms/L versus 50 micrograms/L, respectively; p<.02). In addition, infants born with neural tube defects had significantly lower selenium levels compared to healthy newborns (median 26 micrograms/L versus 33 micrograms/L in cord blood, respectively; p<.01).[24]
    - Similar results were found in another study conducted in Turkey. One hundred mothers of neonates with neural tube defects had significantly lower serum selenium levels than a comparison group of 70 mothers with healthy neonates (55 micrograms/L versus 80 micrograms/L, p<.0001). In this study, mothers of babies with neural tube defects also had significantly higher levels of the heavy metals arsenic, lead, and cadmium.[25]
- **Higher maternal selenium is associated with improved neurological development in infants and children**
    - Higher maternal selenium levels during 1st trimester of pregnancy were associated with significantly higher language and motor skills in 1 yr old infants (p=.005).[26]
    - In a study of 750 mother-infant pairs from rural Bangladesh, higher maternal erythrocyte selenium levels in *late pregnancy (week 30 gestation)* were positively associated with children's cognitive development at 1.5 yrs of age. Higher maternal selenium status was associated with higher language comprehension, especially in boys, and with higher psychomotor development, especially in girls.[27]
    - A follow-up study of these children in Bangladesh by investigators at the Karolinska Institute revealed higher maternal erythrocyte selenium levels in *early pregnancy (week 14 gestation)* were associated with higher cognitive function at 5 and 10 yrs of age.[28]
    - Deficits in executive function are increasingly recognized in preterm neonates. In a study of executive function in Chinese preterm infants evaluated at 8 months of age, particular deficits in executive function seen in preterm infants — namely working memory and inhibition — were significantly associated with lower maternal selenium status.[29]
    - In a study of 927 newborns in Shanghai, China, *both low and high* umbilical cord blood selenium levels were associated with an adverse effect on Neonatal Behavioral Neurological Assessment (NBNA) score at 3 days of age. This U-shaped dose-response between cord blood selenium and fetal neurobehavioral development indicated an optimum of 100 micrograms/L.[30]

Selenium and Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome with symptom onset before 3 years of age. The hallmark of ASD is impairment of social interaction and communicative ability, coupled with restricted and repetitive behaviors, and varying degrees of intellectually disability. Besides a strong male predisposition, risk factors include parental age, preterm birth, short interpregnancy interval, and prenatal exposure to air pollution.[31]

EVIDENCE FROM GENETIC STUDIES

- In a study conducted in the USA, investigators evaluated the association between ASD and a variant of the GPX1 gene, which encodes for the antioxidant selenoenzyme glutathione peroxidase 1.[32] A particular variant of the gene was significantly undertransmitted from parents to offspring affected with autistic disorder compared to unaffected offspring, suggesting that possession of this allele may be protective for ASD. No consistent abnormality in enzyme activity is associated with this variant. The difficulty in characterizing the shifting genetic landscape of ASD is compounded by the growing recognition that ASD phenotypes are not fixed, but instead their severity may be significantly influenced by interventions.[33]

EVIDENCE FROM OBSERVATIONAL STUDIES

- Twenty children in Ontario with ASD (average age, 4yrs) were found to have 15% lower erythrocyte selenium levels compared to 15 healthy age-matched controls ($p<.0006$).[34]
- In a study conducted in Saudi Arabia, 35 children with ASD (average age, 7.2 yrs) had 42% lower erythrocyte selenium levels compared to 30 healthy age-matched controls ($p<.001$).[35]
- In a study conducted in Russia, 70 children with ASD had a non-significant 11% lower serum level compared to 70 age- and gender-matched controls ($p=.39$).[36]
- In a recent review article, the results of 11 independent studies indicated that ASD cases have disrupted glutathione metabolism, leading to consistently lower plasma levels of reduced glutathione.[37] Selenium, as a component of selenoenzymes, plays an important role in restoring reduced glutathione. The activity of glutathione as an intracellular antioxidant is essential for redox control that promotes normal brain development, preventing or limiting the extent of oxidative damage to brain and other neuroendocrine tissues.
- **One possible mechanism might be selenium's ability to counteract heavy metal toxicity**
    - In the Russian study described above,[47] increased erythrocyte levels of lead (Pb) and mercury (Hg) were reported in children with ASD, resulting in a significant decrease in ratios of Se:Pb and Se:Hg ($p<.001$). Since selenium is known to have neuroprotective effects, in part due to its antagonistic effect on mercury, the investigators state their study "indicates the importance of selenium for prevention and/or therapy of heavy metal neurotoxicity."
    - As for how selenium helps to protect against heavy metals, at least one mechanism is selenium binding to heavy metals. For example, mercury binds to selenium with extraordinarily high affinity, and mercury has been shown to inhibit selenium-dependent enzyme activities in fetal brain. It appears that increased maternal dietary selenium consumption can preserve selenium-dependent enzymatic activities, thereby limiting pathological effects.[38] Studies have demonstrated the binding of complexes of mercury-selenium, silver-selenium, and cadmium-

selenium in plasma by selenoprotein P, suggesting that selenoprotein P may function as an important chelator of heavy metals, limiting their toxicity.

- Selenium has also been shown to have an antagonistic effect on cadmium, another heavy metal.[39] In one study conducted in the USA, higher maternal toenail cadmium levels were associated with a nearly two-fold increase (p=.13) in intrauterine growth restriction (IUGR), defined as fetal weight below the 10th percentile for gestational age. This relationship between cadmium and IUGR strengthened to more than a three-fold increase in women with lowest selenium status. Overall, higher maternal toenail selenium levels were associated with a significant reduction in risk for IUGR (73% reduction per interquartile range increase in selenium, p=.045). Median maternal toenail selenium concentration was .97 ppm (IQR, .23 ppm).
- In a study of community-dwelling Brazilians age 15 to 87 years, people with higher mercury levels had lower performance on tests of motor function (p<.01). Interestingly, the beneficial effects of higher plasma selenium levels on motor function were seen most consistently in individuals with the highest mercury levels.[40]

- Whether maternal selenium supplementation can reduce the incidence of ASD has not yet been studied, yet when considering the available evidence, it would be prudent to ensure women desiring to become pregnant, or are pregnant, have adequate selenium intake.

Consideration of Selenium Form

- Although the FDA does not recommend a particular form of selenium to be added, a recent review indicates that organically bound selenium (e.g., high-selenium yeast, selenomethionine) is better absorbed and retained compared to inorganic forms (e.g., selenite, selenate) and, based upon preliminary data from adults, standardized high-selenium yeast may offer greater benefits than other forms of organically bound selenium.[41] For example, women in Finland given 100 micrograms of selenium daily from high-selenium yeast during lactation had significantly higher selenium concentration in their breast milk than women given the same amount of selenium, but in the form of selenite (p<.03).[42]
- Current evidence suggests that selenium from selenium yeast is 1.5 to 2 times more bioavailable than inorganic forms, selenite and selenate, which even though they are well absorbed are not retained in the body as long as organic selenium.[43]
- A direct comparison between the impact of standardized selenium-yeast SelenoExcell® and selenomethionine on two urinary markers of oxidative stress (8OHdG and 8-Isoprostane) was made in a small randomized intervention trial in men performed by a Pennsylvania State University research team.[44] Nine months of supplementation with SelenoExcell® was associated with a significant decrease in these markers of oxidative stress compared to placebo-treated subjects. Men supplemented with selenomethionine did not show a significant decrease in oxidative stress markers.
- In a study conducted in the USA, selenium status of infants was significantly affected by method of feeding (breastfeeding versus bovine milk-based infant formula) and the amount of dietary selenium intake. The authors found no clear-cut superiority between the advantages that were gained through two different maternal selenium supplementation strategies, which compared two forms of organic selenium (selenomethionine versus selenium-yeast).[45]
- Maternal supplementation with high-selenium yeast has been shown to significantly reduce risk for preterm birth[6] and preeclampsia[18]; no studies using other organic forms of selenium or using selenite have documented this beneficial effect.

Optimizing Selenium Intake for Maternal and Infant Health

Selenium is an essential nutrient functioning through 25 different selenoproteins. These selenoproteins play critical roles in promoting health through antioxidant protection, DNA synthesis, reproduction, thyroid hormone production and metabolism, as well as immune function.[46] The Recommended Dietary Allowance (RDA) for selenium is based on the amount needed to maximize synthesis of the selenoprotein glutathione peroxidase, as assessed by a plateau in the activity of GPX3, the isoform of this enzyme found in plasma.[47] Worldwide differences in selenium status reflect significant geographic variations in soil selenium content, which limits selenium intake from foods and may lead to inadequate selenium status. Recommended Dietary Allowances (RDAs) reflect nutrient intakes intended to prevent deficiency signs. Optimizing overall health — the ambitious aim currently under intense pursuit — is a goal that goes beyond merely side-stepping the development of deficiency signs to revealing the level of supplementation required to achieve optimal selenium status.

Recommended Dietary Allowances (RDAs) for Selenium

- The recommendations for dietary selenium intake developed by the Food and Nutrition Board at the Institute of Medicine (IOM) appear in Table 1.[48]

Table 1: Recommended Dietary Allowances (RDAs) for Selenium

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	15 mcg*	15 mcg*		
7–12 months	20 mcg*	20 mcg*		
1–3 years	20 mcg	20 mcg		
4–8 years	30 mcg	30 mcg		
9–13 years	40 mcg	40 mcg		
14–18 years	55 mcg	55 mcg	60 mcg	70 mcg
19–50 years	55 mcg	55 mcg	60 mcg	70 mcg
51+ years	55 mcg	55 mcg		

* Adequate Intake; mcg:microgram

New FDA Regulations for Selenium in Infant Formulas

- In June 2015, the US FDA modified the regulations on nutrient specifications and labeling for infant formula by adding selenium to the list of required nutrients.[49] The regulation now requires that infant formulas contain 2 to 7 micrograms of selenium per 100kcal. This is comparable to the European Food Safety Authority (EFSA) recommendation, which set the minimum and maximum selenium levels at 1 and 9 micrograms of selenium per 100kcal for both infant formula as well as Follow-On Formula,[50] and aligns with the recommendation made by the Scientific Committee on Food (SCF) of 3 to 9 micrograms of selenium per 100kcal infant formula.[51]

APPENDIX: Additional Information on the Mechanisms and Consequences of Preterm Birth

- **Problems associated with preterm births include:**[52]
  - Increased mortality
  - Neurological problems (such as learning disorders, including ADHD)
  - Visual impairment
  - Severe infections
  - Respiratory problems (both acute as well as chronic lung disease)
- **Magnitude and Cost of Preterm Births**
  - Preterm birth rate is the leading cause of death during the first 4 weeks of life.
  - Preterm birth is second only to pneumonia as the cause of death in children under the age of 5 years.[53]
  - Each year, 15 million infants are born preterm world-wide.
  - Preterm birth rate in the USA is 9.63%, affecting over 382,000 newborns each year.[54]
  - Preterm birth rate in the USA increases after age 35 and is highest among women age 45-54 years at more than 23%.
  - In the USA, blacks have the highest preterm birth rate, exceeding 13%.
  - A March of Dimes study conducted in 2007 estimates that on average each preterm birth in the USA costs $51.7K. Annually, preterm births could cost Americans as much as $26.2 billion.
- **How might adequate selenium status reduce preterm births?**
  - ***Helps to maintain antioxidant protection*** through optimizing key antioxidant enzymes, such as glutathione peroxidase (GPx), which in turn can help maintain uteroplacental circulation. It should be noted that in two randomized clinical trials conducted in the USA[55] and Brazil,[56] supplementation with vitamin E and vitamin C did not significantly reduce risk of spontaneous preterm birth.
  - ***Helps to optimize immunity*** so as to help protect against infection which is a major cause of preterm birth,[8] while also helping to regulate the inflammatory response.
  - ***Helps to reduce gestational diabetes mellitus*** as fasting blood glucose concentration has been found to be inversely correlated to plasma selenium concentration[57] and diabetes mellitus increases the risk of preterm births as 17% of babies born to diabetic mothers in the UK were preterm as compared to 4-7% in the general population.[58]
  - ***Helps to reduce preeclampsia***, a known risk factor for preterm birth.
  - ***Helps to increase heme oxygenase-1*** via the selenoenzyme thioredoxin reductase, which is vitally important for:
    - Successful placentation
    - Maintenance of uterine quiescence
    - Regulation of hemodynamic control within the uterus and placenta
    - Protection against ischemia-reperfusion injury and preeclampsia
    - Antioxidant protection and anti-inflammatory effects
  - ***Helps to neutralize effects of environmental pollutants, such as lead, which have been linked to preterm births.***[59]
  - ***Helps to maintain fetal membranes;*** excess superoxide anion can activate matrix metalloproteinase enzymes that favor the degradation of collagen and premature rupture of membranes.[60,61]

References:

[1] Lackritz EM, Wilson CB, Guttmacher AE et al. *A solution pathway for preterm birth: accelerating a priority research agenda*. **Lancet Glob Health** 2013;1:e328-30.

[2] Zhang G, Feenstra B, Bacelius J et al. *Genetic associations with gestational duration and spontaneous preterm birth.* **New Engl J Med** 2017;377:1156-67.

[3] Rayman MP, Wijnen H, Vader H et al. *Maternal selenium status during early gestation and risk for preterm birth.* **CMAJ** 2011;183:549-55.

[4] WHO. **Born Too Soon: The Global Action Report on Preterm Birth**, 2012.

[5] Hurst R, Siyame EWP, Young SD et al. *Soil-type influences human selenium status and underlies widespread selenium deficiency risks in Malawi.* **Sci Rep** 2013;3:1425.

[6] Tara F, Rayman MP, Boskabadi H et al. *Selenium supplementation and premature (pre-labour) rupture of membranes: A randomized double-blind placebo-controlled trial.* **J Obstet Gynaecol** 2010;30:30-4.

[7] Staff AC, Benton SJ, von Dadelszen P et al. *Redefining preeclampsia using placenta-derived biomarkers*. **Hypertension** 2013; 61:932-42.

[8] Roberts JM and Bell MJ. *If we know so much about preeclampsia, why haven't we cured the disease?* **J Reprod Immunol** 2013; 99:1-9.

[9] Moses EK, Johnson MP, Tømmerdal L et al. *Genetic association of preeclampsia to the inflammatory response gene SEPS1*. **Am J Obstet Gynecol** 2008; 198:336.e1-5.

[10] Curran JE, Jowett JB, Elliott KS et al. *Genetic variation in selenoprotein S influences inflammatory response*. **Nature Genetics** 2005; 37:1234-41.

[11] Yong HEJ, Murthi P, Brennecke SP et al. *Genetic approaches to preeclampsia*. **Methods Mol Biol** 2018; 1710: 53-72.

[12] Rayman MP, Bode P, Redman CW. *Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom.* **Am J Obstet Gynecol** 2003;189:1343-9.

[13] Vanderlelie JJ, Perkins AV. *Selenium and preeclampsia: a global perspective*. **Pregnancy Hypertens** 2011;1:213–24.

[14] Mistry HD, Gill CA, Kurlak LO et al. *Association between maternal micronutrient status, oxidative stress, and common genetic variants in antioxidant enzymes at 15 weeks' gestation in nulliparous women who subsequently develop preeclampsia.* **Free Radic Biol Med** 2015; 78:147-155.

[15] Tara F, Maamouri G, Rayman MP et al. *Selenium supplementation and the incidence of preeclampsia in pregnant Iranian women: a randomized, double-blind, placebo-controlled pilot trial.* **Taiwan J Obstet Gynecol** 2010;49:181-7.

[16] Mokhber N, Namjoo M, Tara F et al. *Effect of supplementation with selenium on postpartum depression: a randomized double-blind placebo-controlled trial.* **J Maternal-Fetal Neonatal Med** 2011;24:104-8.

[17] Han L, Zhou SM. *Selenium supplement in the prevention of pregnancy induced hypertension*. **Chinese Med J** 1994; 107:870-1.

[18] Rayman MP, Bath SC, Westaway J et al. *Selenium status in UK pregnant women and its relationship with hypertensive conditions of pregnancy.* **Br J Nutr** 2015;113:249-58.

[19] Catov JM et al. *Association of periconceptual multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort.* **Am J Epidemiol** 2009; 169:1304-11.

[20] Makhoul IR, Sammour RN, Diamond E et al. *Selenium concentrations in maternal and umbilical cord blood at 24-42 weeks of gestations: basis for optimization of selenium supplementation to premature infants.* **Clin Nutr** 2004; 23:373-81.

[21] Germano R, Freitas BON, Nogueira RJN et al. *Selenium deficiency and the effects of supplementation on preterm infants.* **Rev Paul Pediatr** 2014;32:126-35.

[22] Aggarwal R, Gathwala G, Yadav S, Kumar P. *Selenium supplementation for prevention of late-onset sepsis in very low birth weight preterm neonates.* **J Trop Pediatr** 2016;62:185-93.

[23] Bogye G, Alfthan G, Machay T, Zubovics L. *Enteral yeast selenium supplementation in preterm infants.* **Arch Dis Child Fetal Neonatal Ed** 1998;78:F225-6.

[24] Guvenc H, Karatas F, Guvenc M et al. *Low levels of selenium in mothers and their newborns in pregnancies with a neural tube defect.* **Pediatrics** 1995;95:879-82.

[25] Demir N, Baaranoglu M, Huyut Z et al. *The relationship between mother and infant plasma trace element and heavy metal levels and the risk of neural tube defect in infants.* **J Matern Fetal Neonatal Med** 2017;3:1-8.

[26] Polanska K, Hanke W, Krol A. *Micronutrients during pregnancy and child psychomotor development: opposite effects of zinc and selenium.* **Environ Res** 2017;158:583-9.

[27] Skroder HM, Hamadani JD, Tofail F et al. *Selenium status in pregnancy influences children's cognitive function at 1.5 years of age.* **Clin Nutr** 2015;34:923-30.

[28] Skroder H, Kippler M, Tofail F, Vahter M. *Early-life selenium status and cognitive function at 5 and 10 yrs of age in Bangladeshi children.* **Environ Health Perspect** 2017;125:117003.

[29] Feng Y, Zhou H, Zhang Y et al. *Comparison in executive function in Chinese preterm and full-term infants at eight months.* **Front Med** 2017; doi: 10.1007/s11684-017-0540-9.

[30] Yang X, Yu X, Fu H et al. *Different levels of prenatal zinc and selenium had different effects on neonatal neurobehavioural development.* **Neurotoxicology** 2013;37:35-9.

[31] Lyall K, Croen L, Daniels J et al. *The changing epidemiology of autism spectrum disorders*. **Annu Rev Public Health** 2017; 38:81-102.

[32] Ming X, Johnson WG, Stenroos ES et al. *Genetic variant of glutathione peroxidase 1 in autism*. **Brain Development** 2010; 32:105-9.

[33] Huguet G, Ey E, Bourgeron T. *The genetic landscapes of autism spectrum disorders*. **Annu Rev Genomics Hum Genet** 2013; 14:191-213.

[34] Jory J, McGinnis WR. *Red-cell trace minerals in children with autism*. **Am J Biochem Biotechnol** 2008;4:101-4.

[35] El-Ansary A, Bjorklund G, Tinkov AA et al. *Relationship between selenium, lead, and mercury in red blood cells of Saudi autistic children.* **Metab Brain Dis** 2017;32:1073-80.

[36] Skalny AV, Simashkova NV, Skalnaya AA et al. *Assessment of gender and age effects on serum and hair trace element levels in children with autism spectrum disorder.* **Metab Brain Dis** 2017;32:1675-84.

[37] Raymond RJ, Deth RC, Ralston NVC. *Potential role of selenoenzymes and antioxidant metabolism in relation to autism etiology and pathology.* **Autism Res Treatment** 2014; doi: 10.1155/2014/164938..

[38] Berry MJ, Ralston NVC. *Mercury Toxicity and the Mitigating Role of Selenium*. **Eco Health** 2008;5:456-59.

[39] Everson TM, Kappil M, Hao K et al. *Maternal exposure to selenium and cadmium, fetal growth, and placental expression of steroidogenic and apoptotic genes.* **Environ Res** 2017;158:233-44.

[40] Lemire M, Fillion M, Frenette B et al. *Selenium from dietary sources and motor functions in the Brazilian Amazon.* **Neuro Toxicology** 2011;32:944-53.

[41] Lonnerdal B, Vargas-Fernandez E, Whitacre M. *Selenium fortification of infant formulas: does selenium form matter?* **Food Funct** 2017;8:3856-68.

[42] Kumpulainen J, Salmenpera L, Siimes MA et al. *Selenium status of exclusively breast-fed infants as influenced by maternal organic or inorganic selenium supplementation.* **Am J Clin Nutr** 1985;42:829-35.

[43] Rayman MP. *The use of high-selenium yeast to raise selenium status: how does it measure up?* **Br J Nutr** 2004; 92:557-73.

[44] Richie Jr JP, Das A, Calcagnotto AM et al. *Comparative effects of two different forms of selenium on oxidative stress biomarkers in healthy men: a randomized clinical trial*. **Cancer Prev. Res** 2014;7:796–804.

[45] McGuire MK, Burgert SL, Milner JA et al. *Selenium status of infants is influenced by supplementation of formula or maternal diets*. **Am J Clin Nutr** 1993;58:643-8.

[46] Sunde RA. *Selenium*. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, (eds) **Modern Nutrition in Health and Disease** (11th ed). Philadelphia, PA: Lippincott Williams & Wilkins; 2012:225-37.

[47] Institute of Medicine, Food and Nutrition Board. **Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids**. National Academy Press, Washington, DC, 2000.

[48] Institute of Medicine, Food and Nutrition Board. **Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids**. National Academy Press, Washington, DC, 2000.

[49] FDA, HHS, Infant Formula: *The addition of minimum and maximum levels of selenium to infant formula and related labeling requirements. Final Rule.* **Fed Regist** 2015;80;35834-41.

[50] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA*). Scientific opinion on the essential composition of infant and follow-on formulae.* **EFSA J** 2014;12:3760.

[51] Scientific Committee on Food (SCF). *Report of the Scientific Committee on Food on the revision of essential requirements of infant formulae and follow-on formulae*. 2003.

[52] Hodek JM, von der Schulenburg JM, Mittendorf T. *Measuring economic consequences of preterm birth – methodological recommendations for the evaluation of personal burden on children and their caregivers.* **Health Economics** 2011;1:6.

[53] Goldenberg RL, Culhane JF, Iams JD et al. *Epidemiology and causes of preterm birth.* **Lancet** 2008;371:75-84

[54] *Births: Final Data for 2015.* **National Vital Statistics Reports** 2017;66:1-71.

[55] Hauth JC, Clifton RG, Roberts JM et al. *Vitamin C and E supplementation to prevent spontaneous preterm birth: a randomized controlled trial*. **Obstet Gynecol** 2010; 116:653-8.

[56] Spinnato JA, Freire S, Pinto e Silva JL et al. *Antioxidant supplementation and premature rupture of the membranes: a planned secondary analysis*. **Am J Obstet Gynecol** 2008;199: 433e.1-433e.8.

[57] Hawkes WC, Alkan Z, Lang K, King JC. *Plasma selenium decrease during pregnancy is associated with glucose intolerance.* **Biol Trace Elem Res** 2004;100:19-29.

[58] Steer P. *The epidemiology of preterm labor.* **Br J Obstet Gynecol** 2005;112(suppl 1):1-3.

[59] Ferguson KK and Chin HB. *Environmental chemicals and preterm birth: biological mechanisms and state of the science*. **Curr Epidemiol Rep** 2017; 4: 56-71.

[60] Rood KM, Buhimschi IA, Rodewald Millen K et al. *Evidence for participation of neutrophil gelatinase-associated lipocalin/matrix metalloproteinase-9 (NGAL•MMP-9) complex in the inflammatory response to infection in pregnancies complicated by preterm birth*. **Am J Reprod Immunol** 2016; 76:108-17.

[61] Buhimschi IA, Kramer WB, Buhimschi CS, et al. *Reduction-oxidation (redox) state regulation of matrix metalloproteinase activity in human fetal membranes.* **Am J Obstet Gynecol** 2000; 182:458-64.