

Selenium deficiency and the effects of supplementation on preterm infants

Deficiência de selênio e os efeitos da suplementação em prematuros

Deficiencia de selenio y los efectos de la suplementación en prematuros

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ABSTRACT

Objective: This study aimed to review the literature about blood concentrations of selenium associated with gestational age, feeding, supplementation and related clinical features in preterm infants.

Data sources: Systematic review in the following databases: MEDLINE, PubMed, Google academics, SciELO.org, ScienceDirect (Elsevier) and CINAHL-Plus with Full Text (EBSCO). Articles published up to January 2013 with the keywords “selenium deficiency”, “selenium supplementation”, “neonates”, “infants”, “newborn” and “preterm infants” were selected.

Data synthesis: The studies reported that low blood selenium levels are associated with increased risk of respiratory diseases. Preterm infants, especially with low birth weight, presented lower selenium levels. Selenium deficiency has also been associated with the use of oral infant formula, enteral and parenteral nutrition (with or without selenium addition). The optimal dose and length of selenium supplementation is not well-established, since they are based only on age group and selenium ingestion by breastfed children. Furthermore, the clinical status of the infant affected by conditions that may increase oxidative stress, and consequently, selenium requirements is not taken into account.

Conclusions: Prematurity and low birth weight can contribute to low blood selenium in premature infants. Selenium supplementation seems to minimize or prevent clinical complications caused by prematurity.

Key-words: review; selenium; supplementation; infant, newborn; infant, premature.

RESUMO

Objetivo: Revisar os trabalhos que analisaram as concentrações sanguíneas de selênio associadas à idade gestacional, à alimentação, à suplementação e ao quadro clínico de prematuros.

Fontes de dados: Revisão sistemática da literatura por meio de buscas eletrônicas nas seguintes bases de dados: MEDLINE PubMed, Google acadêmico, SciELO.org, ScienceDirect (Elsevier) e CINAHL-Plus with Full Text (EBSCO). Buscaram-se trabalhos publicados até janeiro de 2013 com as seguintes palavras-chave: “*selenium deficiency*”, “*selenium supplementation*”, “*neonates*”, “*infants*”, “*newborn*” e “*preterm infants*”.

Síntese dos dados: Os estudos relataram que os baixos níveis selênio associam-se ao risco aumentado para doenças respiratórias. Os prematuros, principalmente com baixo peso ao nascer, apresentam os menores níveis de selênio. A deficiência do mineral tem sido associada ao uso de fórmula infantil oral, nutrição enteral e parenteral (com e sem adição de selênio). A dosagem e o tempo ideal para a suplementação de selênio ainda não estão bem estabelecidos, visto que se baseiam apenas na faixa etária e na ingestão do mineral por crianças amamentadas no peito. Além disso, não se considera o quadro clínico do recém-nascido, que pode ser acometido de doenças que aumentam o estresse oxidativo e, consequentemente, elevam as necessidades de selênio.

Conclusões: A prematuridade e o baixo peso ao nascer podem contribuir para reduzir as concentrações sanguíneas de selênio em prematuros. A suplementação parece minimizar ou prevenir as complicações clínicas causadas pela prematuridade.

Palavras-chave: revisão; selênio; suplementação; recém-nascido; prematuro.

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RESUMEN

Objetivo: Revisar los trabajos que analizaron las concentraciones sanguíneas de selenio asociadas con la edad gestacional, alimentación, suplementación y cuadro clínico de prematuros.

Fuentes de datos: Revisión sistemática de la literatura mediante búsquedas electrónicas en las bases de datos a continuación: Medline Pubmed, Google académico, SciELO.org, ScienceDirect (Elsevier) y CINAHL with Full Text (EBSCO). La búsqueda se realizó con trabajos publicados hasta enero de 2013 con las palabras clave a continuación: *selenium deficiency, selenium supplementation, neonates, infants, newborn and preterm infants*.

Síntesis de los datos: Los estudios relataron que los bajos índices de selenio están asociados al riesgo aumentado para enfermedades respiratorias. Los prematuros, principalmente con bajo peso al nacer, presentan los menores niveles de selenio. La deficiencia de selenio viene siendo asociada al uso de fórmula infantil oral, nutrición enteral y parenteral (con y sin adición de selenio). La dosis y el tiempo ideal para la suplementación de selenio todavía no están bien establecidos, puesto que se basan solamente en la franja de edad y en la ingestión de selenio de niños amamantados al pecho. Además, no se considera el estado clínico del recién nacido, que puede ser acometido por enfermedades que aumentan el estrés oxidativo y, por consiguiente, elevan las necesidades de selenio.

Conclusiones: La prematuridad y el bajo peso al nacer pueden contribuir para reducir las concentraciones sanguíneas de selenio en prematuros. La suplementación parece reducir o prevenir las complicaciones clínicas causadas por la prematuridad.

Palabras clave: revisión sistemática; deficiencia de selenio; suplementación de selenio; recién nacido; prematuro.

Introduction

Selenium is a trace element considered essential due to its participation in major metabolic functions^(1,2), immune system, thyroid hormone metabolism^(1,2), male infertility, neoplasms and cardiovascular disease⁽²⁾. It also has antioxidant properties^(1,3).

Selenium is an active-site component of glutathione peroxidase (GPx)⁽⁴⁾. This enzyme contains four atoms of selenium and is responsible for nearly 30% of plasma selenium levels^(1,5). GPx has antioxidant function⁽³⁾, thereby protecting

body cells from oxidation and reducing toxic substances caused by oxidative stress⁽⁶⁾.

In 1979, it was discovered that selenium supplementation could prevent the appearance of Keshan disease, a cardiomyopathy affecting children living in regions of selenium-deficient soil⁽⁷⁾. In the pediatric population, selenium deficiency is most commonly found in preterm infants, associated with gestational age, feeding after birth and clinical status⁽⁸⁻¹⁰⁾.

According to the National Health and Medical Research Council (NH&MRC, 2006)⁽¹¹⁾, the daily recommended oral dose of selenium is 12–15 µg. For enteral nutrition, the recommended dose is 1.3–3.0 µg/kg/day. For parenteral nutrition, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, 2005)⁽¹²⁾ has recommended the administration of 2–3 µg/kg/day. Currently, the American Society for Parenteral and Enteral Nutrition (ASPEN, 2012)⁽¹³⁾ suggested an improvement of recommended intake of selenium from 20–60 µg/day to 60–100 µg/day for adults. With respect to pediatric patients, including neonates, the recommended dose remained 2 µg/kg/day⁽¹³⁻¹⁶⁾.

The addition of selenium to oral, enteral and parenteral infant formulas is not a routine practice in all countries and health care services. In Brazil, selenium is not routinely added to parenteral nutrition, despite studies reporting that selenium supplementation may prevent or correct a deficiency in this mineral⁽¹⁷⁻¹⁹⁾.

This study aimed to review the literature about blood selenium concentrations in preterm infants associated with gestational age, feeding, supplementation and related clinical features.

Method

A systematic review was conducted by electronic search. Medline Pubmed, Google Scholar and Capes Platform databases were used for a refined search in the following databases: SciELO.org, ScienceDirect (Elsevier) and CINAHL-Plus with Full Text (EBSCO). Searches were made of studies published up to January, 2013 with the following keywords: *selenium deficiency, selenium supplementation, neonates, newborn, preterm infants*. No limitations were applied regarding date of publication and language. The exclusion criteria were as follows: review papers, animal research, studies with dead children and studies with inadequate age group. For data collection, Boolean operators that broadened or restricted the number of articles identified by the search system were used.

Table 1 - Type of study, location, case study, feeding form and conclusion in selected studies

Author/year	Type of study	Country	Population	Feeding
Amin <i>et al</i> , 1980 ⁽²⁸⁾	Study 1: Cross-sectional Study 2: Longitudinal	USA	Study 1: 68 preterm infants (GA 28–36wks.), 18 term infants, 50 normal children. Study 2: 8 preterm infants with severe respiratory insufficiency. Assessment until the 6 th wk of age.	PN and F
Lockitch <i>et al</i> , 1989 ⁽²¹⁾	Prospective observational longitudinal	Canada	Baseline: 56 healthy term newborns and 39 LBW infants with a mean (SD) BW of 1940±257g and 35 VLBW infants of 1064±264g with <37wks. of gestation. Assessment until the 7 th wk of life in 16 preterm infants.	PN (without Se) with or without oral intake.
Huston <i>et al</i> , 1991 ⁽⁴⁷⁾	Prospective Randomized Clinical Trial	USA	20 preterm infants (BW<1000 g). The mean (SD) GA in G1=26.7±1.5 and G2=26.5±1.2 wks. Assessment until the 60th day.	PN and EN. G1 (n = 10; 1.34µg/kg/day of selenious acid) and G2 (without Se).
Smith <i>et al</i> , 1991 ⁽²⁹⁾	Prospective Clinical Trial	USA	46 preterm infants (BW<1700 g). The mean GA was 29.3 weeks. Assessment until the 3th wk of life.	BF (n=21; 24ng Se/mL), F (n=13; 7.8 ng Se/mL), and F (n=12; 34.8 ng Se/mL). (Not differentiated)
Mask <i>et al</i> , 1993 ⁽²⁷⁾	Cross-sectional	USA	13 preterm newborns (Mean (SD) BW and GA was 1869±449g and 33.5±1.8wks.), 15 term newborns and their mothers and 15 women who were not pregnant.	
Darlow <i>et al</i> , 1995 ⁽³²⁾	Prospective observational longitudinal	New Zealand	79 preterm newborns with a mean (SD) GA of 28.3±2.5wks. And BW of 1164±254g. Assessment until the 28 th day of life.	PN (without Se), EN and BF or F.
Daniels <i>et al</i> , 1996 ⁽¹⁸⁾	Prospective Randomized Clinical Trial	Australia	Preterm newborns (G1: 19 and G2: 19) healthy term newborns (RG=32). The mean (SD) BW and GA were 1171±38g and 29±0.3wks. Assessment until the 6th wk of life.	G1:PN (without Se), G2:PN (3µg/kg/day of selenious acid) and RG (F and BF).
Bogye <i>et al</i> , 1998 ⁽⁵¹⁾	Randomized Clinical Trial	Hungary	36 preterm newborns with VLBW. BW of 975±122g and GA 27±1wk. Supplementation for 14 days.	G1 (n=18): (nasogastric EN by drip) with 4.8mg yeast (5µg of Se) G2 (n=18): not supplied
Bogye <i>et al</i> , 1998 ⁽³⁸⁾	Randomized Clinical Trial	Hungary	28 preterm newborns with birth weight and GA of 962±129g and 27±1wk. Supplementation for 14 days.	G1 (n=14): (nasogastric EN by drip) with 4.8mg of yeast (5µg of Se). G2 (n=14): not supplied
Merz <i>et al</i> , 1998 ⁽⁴⁰⁾	Prospective	Germany	34 VLBW infants with GA and BW 28.6±2.5wks. and 1075±249g respectively. Assessment until 4 th wk of life.	Mainly PN and were not specifically supplied with Se.
Klinger <i>et al</i> , 1999 ⁽³⁹⁾	Cross-sectional	Israel	29 VLBW infants with mean (SD) age and weight 26±1.7wks and 809±129g	Se: 2µg/kg/d selenious acid.
Darlow <i>et al</i> , 2000 ⁽²⁴⁾	Double-blind placebo-controlled randomized Trial	New Zealand	534 infants with BW<1500g Assessment until 36wks of life.	PN: 7µg/kg/d and F: 5µg/kg/day sodium selenite.

Continue...

Table 1 - Continuation

Author/year	Type of study	Country	Population	Feeding
Winterbourn <i>et al</i> , 2000 ⁽⁴⁸⁾	Randomized controlled Trial	New Zealand	173 newborns with weight <1500g. Assessment until 36wks of life.	PN: 7µg/kg/d and F: 5µg/kg/day sodium selenite.
Sievers <i>et al</i> , 2001 ⁽⁴⁵⁾	Prospective observational longitudinal	Germany	16 preterm newborns (GA 25–32wk and BW 595–1495g), 14 term newborns with F and 17 term newborns with BF. Assessment until 1 st year of life.	BF, F and complementary feeding.
Makhoul <i>et al</i> , 2004 ⁽⁸⁾	Cross-sectional	Israel	165 preterm newborns and term newborns (24–42wks.) and their mothers.	(Not differentiated)
Mentro <i>et al</i> , 2004 ⁽⁹⁾	Prospective observational longitudinal	14 Caucasians, 3 Hispanics and 1 Asian-American	18 preterm newborns with BW of 1013g (650–1370g) and risk of BPD. Mean GA was 27 weeks. Assessment until 4 th week of life.	BF, PN, EN and F. Mean ingestion of Se in the 1 st wk was 0.82µg/kg/day and 1.7µg/kg/day in the 4 th wk.
Galinier <i>et al</i> , 2005 ⁽³⁰⁾	Cross-sectional	France	248 preterm newborns and 262 term newborns. The mean GA and BW (SD) for preterm newborns was 32.4±2.52wks. and 1845±489g.	(Not differentiated)
Nassi <i>et al</i> , 2009 ⁽¹⁰⁾	Prospective observational longitudinal	Italy	30 preterm infants with mean (SD) BW and GA of 1605±122 g and 34.5±0.5 wk. The control group included 30 term infants. Assessment until the 100 th day of life.	BF

BF: breastfed; BPD: bronchopulmonary dysplasia; BW: birth weight; EN: enteral nutrition; G: group; GA: gestational age; F: oral infant formula; LBW: low birth weight; PN: parenteral nutrition; RG: reference group; SD: standard deviation; Se: selenium; VLBW: very low birth weight; Wk: week.

One hundred and eighty-nine (189) articles were found. Of these, 18 were selected and 171 excluded (63 repeated studies, 50 animal studies, 14 review articles, 27 with inadequate age group, 11 did not address the topic, 6 reported dead children).

Thus, based on titles and abstracts, 18 studies were chosen for this systematic review. After the selection of studies, level of evidence and grades of recommendation were classified according to Brazilian Medical Association⁽²⁰⁾.

Results

Eighteen articles analyzing selenium concentrations in preterm infants were selected. Table 1 shows study design, population characteristics and forms of feeding. According to the criteria of the Brazilian Medical Association⁽²⁰⁾, studies were classified as A or B. In table 2, a relationship between selenium status and age of the child is observed.

Concerning birth weight, Makhoul *et al*⁽⁸⁾ observed that the lower the weight, the lower the selenium concentration ($r=0.237$; $p=0.002$). Lockitch *et al*⁽²¹⁾ found a significant

correlation between BW and plasma Se ($r=0.47$; $p<0.001$). Plasma GPx levels were more highly correlated with birth weight ($r=0.64$; $p<0.001$). In addition, studies have related alterations in selenium concentration and clinical status (Table 3).

Table 4 shows studies correlating the amount of selenium provided by feeding routes used with selenium concentrations observed in studies of children.

Discussion

It is known that the pediatric population, particularly premature infants⁽⁸⁻¹⁰⁾, is vulnerable to low Se concentrations due to nutritional changes⁽²²⁾, possible clinical complications^(10,23) and low selenium liver stores^(8,9,24-26). This occurs because of immature chorionic villi that acts in the transport of this mineral and also due to inadequate intestinal absorption^(8,9,25,26).

During pregnancy, maternal blood selenium levels decrease, reflecting a greater amount of selenium transported to the fetus in the 3rd trimester of pregnancy. Mask *et al*⁽²⁷⁾, Amin *et al*⁽²⁸⁾ and Smith *et al*⁽²⁹⁾ suggest that low selenium values found in preterm infants must be associated

Table 2 - Main results found in publications about the relationship between alterations in selenium status and age

Author	Results
Amin <i>et al</i> , 1980 ⁽²⁸⁾	The mean serum concentration in term infants (0.098±0.025µg/mL) was slightly higher than preterm infants (0.032 µg/ml), but there was not difference significant.
Lockitch <i>et al</i> , 1989 ⁽²¹⁾	The mean concentration decreased from 0.74±0.13 to 0.63±0.15µmol/L at day 7 (p=0.01) and at day 14 decreased to 0.51±0.19µmol/L (p<0.001). Se values decreased in all 16 preterm infants followed over the first 50 days. In 11 infants, levels dropped to <0.22µmol/L (17µ/L).
Smith <i>et al</i> , 1991 ⁽²⁹⁾	After 3 th week there were no significant differences of Se concentration between groups (preterm infants with F and BF).
Mask <i>et al</i> , 1993 ⁽²⁷⁾	The plasma Se was lower in preterm newborns (0.08±0.02µg/mL) than term newborns (0.10±0.02µg/ml), p=0.052.
Darlow <i>et al</i> , 1995 ⁽³²⁾	There was no significant correlation between gestational period and plasma Se. The correlations among GPx and plasma Se was weak at birth (0.39) and at 28 days (0.17).
Merz <i>et al</i> , 1998 ⁽⁴⁰⁾	After birth the value of plasma Se was 34.2µg/L and reduced to 16.1µg/L after 4 weeks (p<0.001).
Klinger <i>et al</i> , 1999 ⁽³⁹⁾	No correlation was observed between the plasma Se and gestational age (r=0.27, p=0.16). There was significant correlation between gestational age and the level of T4 (r=0.45; p=0.02).
Winterbourn <i>et al</i> , 2000 ⁽⁴⁸⁾	There was no statistically significant difference in GA between the group with and without Se.
Sievers <i>et al</i> , 2001 ⁽⁴⁵⁾	Plasma Se concentrations in preterm newborns were 11.7 (6.5–20.8)µg/L (assessment in the hospital). At 4 months: preterm newborns = 11.6 (8.8–16.7)µg/L, term newborns fed with IF=31.3 (24.3–47.5)µg/L and term newborns BF=45.6 (27.1–65.1)µg/L.
Makhoul <i>et al</i> , 2004 ⁽⁸⁾	Linear relationship between umbilical cord blood concentrations and GA (r =0.341, p<0.0001).
Mentro, Smith, Moyer-Mileur, 2004 ⁽⁹⁾	Se concentrations decreased from the 1 st to 4 th wk of life. Plasma Se (SD)=0.97±0.21µmol/L in the 1 st wk and 0.72±0.27 µmol/L in the 4 th wk (p=0.001). There was not change in plasma GPx among week 1 and 4. The erythrocyte GPx increased along the time period (t =-3.38; p=0.004) and was associated to the GA.
Galinier <i>et al</i> , 2005 ⁽³⁰⁾	Se concentration increased with GA from 0.4±0.1µmol/L (26 th to 33 rd week) to 0.5±0.1µmol/L (from the 33 rd to the 37 th week) and 0.6±0.1µmol/L (>37 th weeks) (p<0.001, r=0.593).
Nassi <i>et al</i> , 2009 ⁽¹⁰⁾	Up until 20 days postnatal, the GPx was lower in the preterm infants than in the term infants.

BF: breastfed; GA: gestational age; GPx: glutathione peroxidase; Se: selenium.

with selenium accumulation during gestation. This fact was observed in studies by Makhoul *et al*⁽⁸⁾ and Galinier *et al*⁽³⁰⁾, who analyzed umbilical cord selenium concentration and noted a significant association with gestational age of newborn infants. Selenium concentration increased after 36 weeks in the former study and from the 26th to the 38th week in the latter study.

Mentro, Smith and Moyer-Mileur⁽⁹⁾ suggested that pre-term infant's small Se stores are used preferentially for GPx

production, occurring in stable or increased GPx and decreased Se concentrations. This could explain the poor correlation between selenium and GPx concentrations observed in the studies^(9,18,21,24,31). Another possibility is that the natural defenses antioxidant like enzyme GPx, mature along the gestation. So, in premature animal, the GPx probably are poorly developed⁽³²⁾.

According to Daniels, Gibson and Simmer⁽¹⁸⁾ and Mentro, Smith and Moyer-Mileur⁽⁹⁾, GPx concentrations might be

confounded by supplemental oxygen and steroids which are common practice for preterm infants. Thus according to authors, GPx activity may be a poor functional indicator of selenium status in infants^(10,31-33), especially in preterm infants^(8,9,24,32). But GPx, seems to be a good marker for adults^(8,18,32).

Prematurity also affects birth weight⁽³⁴⁾. Birth weight is the anthropometric indicator that has the greatest influence on health and newborn survival^(33,35-37). Makhoul *et al*⁽⁸⁾ and Lockitch *et al*⁽²¹⁾ observed that the lower the weight, the lower the concentration of selenium in newborns. Bogye, Alfthan and Machay⁽³⁸⁾ stated that very low birth weight premature infants are obviously susceptible to selenium deficiency.

Selenium deficiency has also been associated with a greater number of diseases and clinical complications. Klinger *et al*⁽³⁹⁾ found selenium deficiency in most premature infants however, there was not a significant correlation between selenium levels and thyroid hormones.

Merz *et al*⁽⁴⁰⁾ found no relationship between the incidence of bronchopulmonary dysplasia and selenium status. Darlow *et al*⁽²⁴⁾ suggested that low Se concentrations may be associated an increase in risk to lung injury.

Darlow *et al*⁽³²⁾ were the first to demonstrate in humans an association between low plasma selenium levels and a greater risk of lung disease, evidenced by oxygen requirement and dependency in the 28th day of life of the affected patients. Mentro, Smith and Moyer-Mileur⁽⁹⁾ showed that, despite a reduction in selenium plasma levels, increased selenium ingestion was associated with a reduction in oxygen dependency. In fact, selenium supplementation would act against oxidative stress caused by early exposure to an oxygen-rich environment, in addition to supplemental oxygen provided in some cases.

Daniels, Gibson and Simmerb⁽¹⁸⁾ found no significant difference in the incidence of retinopathy of prematurity

Table 3 - Main results found in publications about alterations in selenium concentration and clinical status

Author/year	Results
Darlow <i>et al</i> , 1995 ⁽³²⁾	Between 48h and 28 days of life, it was observed that each 0.1 µmol/L decrease in plasma Se was associated with a 28% increase in the number of days the infants received O ₂ (95%CI -0.5–64; <i>p</i> = 0.06). In the 28th day, plasma Se was significantly lower in preterm newborns with CLD (<i>p</i> <0.001). Mean plasma Se was lower in preterm newborns with BPD. And each 0.1 µmol/L decrease in plasma Se was associated with a 58% increase in days of O ₂ dependency.
Daniels <i>et al</i> , 1996 ⁽¹⁸⁾	When boys were analyzed separately, it was noticed that the incidence of CLD is similar between groups (60% in BW without supplementation and 63% in BW with supplementation).
Merz <i>et al</i> , 1998 ⁽⁴⁰⁾	Se values were not significantly different among the preterm infants with and without BPD.
Klinger <i>et al</i> , 1999 ⁽³⁹⁾	26 infants was diagnosed with Se deficiency (serum levels were <0.72µM). Low values of T4 were found in 10 of the 26 children who also had low levels of Se, but it was not observed low levels of TSH. No correlation was observed between the plasma Se and T4 (<i>r</i> =0.36; <i>p</i> =0.06) or TSH (<i>r</i> =0.06; <i>p</i> =0.76).
Darlow <i>et al</i> , 2000 ⁽²⁴⁾	Before randomization the mean plasma Se was 0.33 µmol/l in both groups. In 28 days it had increased to 0.56µmol/L in the supplemented infants, but had dropped to 0.29µmol/L in the infants without Se (<i>p</i> <0.0001). The lower plasma Se found before randomization was associated with increased respiratory morbidity. After the first week, the infants with lower supplementation had an episode of sepsis (<i>p</i> <0.038).
Winterbourn <i>et al</i> , 2000 ⁽⁴⁸⁾	There was a weak negative correlation with GPx in the 36 th week (correlation coefficient, -0.23, <i>p</i> =0.01). Regarding MDA, there was no correlation with plasma Se and GPx at any given moment. Therefore, Se supplementation did not influence the levels of these markers.
Mentro <i>et al</i> , 2004 ⁽⁹⁾	Se ingestion in the 1 st week was associated with a reduction in O ₂ dependency in the 28 th day.

BPD: bronchopulmonary dysplasia; CLD: chronic lung disease; GPx: glutathione peroxidase; GA: gestational age; LBW: low birth weight; MDA: malone dialdehyde; O₂: oxygen; PN: parenteral nutrition; Se: selenium.

and intraventricular hemorrhage, but observed a higher incidence of sepsis among premature infants without selenium supplementation.

Thus, feeding newborns with an adequate amount of selenium is important to restore and to maintain selenium liver stores⁽⁹⁾, preventing a number of disorders and complications,

as well as to support the appropriate growth and development of newborn infants.

Daniels *et al*⁽³¹⁾ suggest that supplementation should be at least equivalent to the amount of selenium in breast milk of women from the same geographical region; after all, there are some regions where soils are low in selenium,

Table 4 - Main results found in publications about alterations in selenium concentrations and feeding provided

Author/year	Results
Amin <i>et al</i> , 1980 ⁽²⁸⁾	Premature infants without Se supplemented had low Se levels the 2 nd week (0.063µg/mL). But when the preterm infants were fed with formula (with Se), the concentrations increased to 0.079µg/mL the 4 th -6 th week of age.
Huston <i>et al</i> , 1991 ⁽⁴⁷⁾	Se concentrations dropped in infants with and without added Se when PN was discontinued, but were significantly higher in the preterm infants supplemented with EN. GPx demonstrated a significant increase in supplemented group with EN and then tended to fall. In preterm without Se, GPx tended to increase; then dropped significantly when PN was discontinued.
Smith <i>et al</i> , 1991 ⁽²⁹⁾	At the 3 rd week, the plasma Se was greater in preterm infants BF than the preterm infants fed with F ($p<0.05$). There were no differences between groups for GPx concentrations.
Darlow <i>et al</i> , 1995 ⁽³²⁾	A reduction in plasma Se concentration was not significantly correlated with the 28 th day of PN.
Daniels <i>et al</i> , 1996 ⁽¹⁸⁾	Along the 3 weeks, while all newborns received a mean 82% of daily energy by PN, Se plasma decreased in the PN group without Se ($p=0.001$; $n=17$) and maintained the levels in PN with Se. Therefore, in infants without Se, plasma Se levels were significantly lower in the 3 rd week ($p=0.026$). Se plasma concentration was $\leq 10\mu\text{g/L}$ and associated with deficiency symptoms in 24% of the PN group without Se and 13% in the PN group with Se. 3 rd to 6 th week: Among the RG, plasma Se increased in newborns BF ($p=0.001$; $n=23$) and decreased in newborns with F ($p=0.039$; $n=8$). Among preterm newborns, there was no significant change. 6 th week: preterm newborns (with PN) and term newborns (with F) showed a reduction in Se plasma concentration compared to term newborns (with BF) ($p<0.001$). The GPx activity increased in supplemented infants ($p=0.042$) and there was no change in unsupplemented infants ($p=0.264$). There was no difference in GPx among the groups at week 3 and 6.
Bogye <i>et al</i> , 1998 ⁽⁵¹⁾	In the EN group without supplementation, mean serum Se concentration decreased significantly in 2 weeks from $34.4\pm 20.4\mu\text{g/L}$ to $26.1\pm 16.6\mu\text{g/L}$ ($p<0.005$). In the supplemented group, it increased from $36.1\pm 12.8\mu\text{g/L}$ to $43.5\pm 7.9\mu\text{g/L}$ ($p<0.01$).
Bogye <i>et al</i> , 1998 ⁽³⁸⁾	In the EN group without supplementation, the mean serum Se concentration decreased significantly in 2 weeks from 25.9 ± 6.8 to $18.2\pm 6.4\mu\text{g/L}$ ($p<0.004$). In the supplemented group, it increased significantly from 32.1 ± 8.5 to $41.5\pm 6.5\mu\text{g/L}$ ($p<0.004$).
Winterbourn <i>et al</i> , 2000 ⁽⁴⁸⁾	Supplementation resulted in a significant increase in plasma Se, virtually doubling the value compared to values observed before supplementation, with the major part increasing in the first week. Supplementation also prevented a decrease in GPx, already showing a statistically significant difference in the 1 st week between groups. There was no significant difference in carbonyl protein concentrations and MDA between the supplemented group and the non-supplemented group.

BF: breastfed; EN: enteral nutrition; F: oral infant formula; GPx: glutathione peroxidase; MDA: malone dialdehyde; PN: parenteral nutrition; RG: reference group; Se: selenium.

as in New Zealand⁽³²⁾, Switzerland⁽⁴¹⁾, China⁽⁴²⁾ and some states of Brazil⁽⁴³⁾.

Makhoul *et al*⁽⁸⁾ stated that infants fed with maternal milk, regardless of being premature or not, do not require selenium supplementation. However, when feeding of these infants is based on infant formula, enteral or parenteral nutrition, supplementation is necessary even in term newborn infants.

Most publications studied in this review showed an association between feeding provided to infants — infant formulas administered by oral, enteral or parenteral route containing little or no addition of selenium — and low selenium concentrations^(9,18,23,28,31,32,44).

The current recommendations for selenium supplements are based on the ingestion of selenium by infants fed with maternal milk, since it appears to meet newborn requirements^(15,31,33).

Currently, ASPEN (2012)⁽¹³⁾ recommends 2µg/kg/day selenium in parenteral nutrition for the pediatric population. There is no differentiation between preterm and term neonates, healthy and sick neonates, and between neonates with appropriate or low birth weight for gestational age.

Surveys claim that selenium concentrations are lower in preterm infants, especially in those with low birth weight (<1,500 g) and very low birth weight (<1,000g), when compared with term infants^(22,37,38,45,46).

Daniels, Gibson and Simmer⁽¹⁸⁾, studying preterm infants receiving parenteral nutrition, found selenium levels similar to those observed in children with Keshan disease. Huston, Jelen and Vidgoff⁽⁴⁷⁾ concluded that adding 1.34 µg/kg/day of selenium in PN is not adequate for LBW. Those authors additionally suggested that supplementation with 3µg/kg/day of selenious acid was incapable of preventing significant decreases in plasma selenium concentration when compared with term newborn infants fed breast milk⁽¹⁸⁾. This fact is concerning, since, according to the literature, supplementation may revert several clinical complications, although it is not efficient for reverting Keshan disease.

Klinger *et al*⁽³⁹⁾ reported that supplementation of 2µg/kg/day of selenium has not been able to prevent or reverse selenium deficiency. Thus, the authors support the recommendation to review premature infants guidelines. Makhoul *et al*⁽⁸⁾ suggested that measurement of selenium levels recommended in parenteral nutrition should increase twofold (up to 7µg/kg/day).

In a research conducted by Darlow⁽²⁴⁾, supplementation prevented the fall and achieved levels similar to those

reported in term infants fed human milk. So, the authors suggest that VLBW infants should receive sufficient supplementation to achieve levels observed in term infants fed human milk, despite the minimal benefits in the clinical picture found in research.

In a study by Winterbourn *et al*⁽⁴⁸⁾, supplementation (7µg/kg/day and 5µg/kg/day of sodium selenite in parenteral and oral nutrition, respectively) did not have an effect on oxidative stress, although selenium levels almost doubled and GPx showed a significant difference between groups with and without supplementation. This fact may be explained by the inadequate dose of selenium, the late supplementation, and also due to the scant evidence of oxidative stress among premature infants.

Despite the discussion about the optimal dose and length of selenium supplementation, several studies have shown that the addition of selenium may prevent diseases and their complications^(6,17,49,51), including a shortened hospital stay and, consequently, lower financial costs.

Conclusion

Nutritional assessment of selenium status in the body to analyze biochemical indicators and clinical manifestations should be performed, especially in premature newborns who were not breastfed. Blood selenium concentrations are reduced in neonates, especially in those with lower gestational age and birth weight. Furthermore, newborn infants who are not breastfed and supplemented show the lowest selenium levels, including newborns, without any underlying disease. Therefore, supplementation is important in preterm infants who were not breastfed in order to minimize the risks of diseases and complications associated with selenium deficiency, contributing to a healthy growth and development of the child.

The optimal dose and length of selenium supplementation have still not been well-established, since they are based only on age group and selenium ingestion in breastfed children. Furthermore, the clinical status of the infants affected by conditions that may increase oxidative stress and, consequently, increase selenium requirements, was not taken into account.

Thus, studies into this subject area are strictly necessary to encourage selenium supplementation in all countries and healthcare services, for the prevention or reversal of selenium deficiency and the resultant complications in humans, especially among newborn infants.

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