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REVIEW PAPER

EFFECT OF MATERNAL SELENIUM SUPPLEMENTATION ON PREGNANCY IN HUMANS AND LIVESTOCK

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Abstract

Following publications underlining the potential use of selenium (Se) in reducing the risk of prostate, skin, colorectal, liver, mammary and lung cancer, awareness of the importance of Se to human health has markedly increased. Moreover, Se status has been inversely associated with other health problems, such as impaired immune function, arthropathy and cardiomyopathy. The most important and well-known Se functions are represented by cell protection against oxidative stress and regulation of thyroid hormone metabolism. Recently, ongoing studies have focused on the relationship between Se intake and fertility and reproductive pathology, as demonstrated by the finding of low Se levels in blood and placenta of women suffering pre-eclampsia and intrauterine growth retardation. Similar problems have also been investigated in livestock and, since the concentration of Se in different soils and different geographical regions varies, addition of this element to animal feed is often required to prevent Se-deficiency diseases in production animal systems. Furthermore, Se supplementation in cattle and ewes is associated with increased embryo production, higher fetal mass and reduced incidence of retained placenta. However, the beneficial effects of supranutrional diet – above European Commission and Food and Drug Administration recommendations (0.5 and 0.3 mg kg^{-1} dm, respectively), but below the maximum tolerable level established by the National Research Council (5 mg kg^{-1} dm) – are affected by other environmental, nutritional and management factors (source of Se, time and length of the treatment, presence of interfering elements, diet feeding

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pattern). The relationship between Se supplementation and the risk of reproductive diseases are complex but recent developments represent promising results in order to refine dietary recommendations for both humans and livestock and develop effective health strategies.

Key words: selenium, pregnancy, placenta, fetus, humans, livestock.

WPŁYW PODAWANIA SUPLEMENTU SELENU MATCE NA CIĄŻĘ U LUDZI I ZWIERZĄT HODOWLANYCH

Abstrakt

Literatura opisująca zastosowanie selenu (Se) w celu obniżenia ryzyka wystąpienia nowotworów wyraźnie spowodowała wzrost świadomości znaczenia tego pierwiastka dla zdrowia człowieka. Ponadto interesujące jest, że poziom Se koreluje na zasadzie odwrotnej proporcjonalności z innymi problemami zdrowotnymi, takimi jak upośledzenie funkcjonowania układu odpornościowego, artropatia, kardiomiopatia, a nawet śmiertelność. Najważniejsze i najlepiej poznane funkcje selenu to ochrona komórek przed stresem oksydacyjnym i regulacja metabolizmu hormonów tarczycy. Ostatnie badania koncentrują się na związku między spożyciem selenu a płodnością i chorobami związanymi z procesem rozmnażania, który to związek wykazano poprzez oznaczenie niskich zawartości selenu we krwi i łożysku kobiet, u których występuje stan przedrzucawkowy i wewnątrzmaciczne zahamowanie wzrastania. Podobne problemy badano u zwierząt hodowlanych; ponieważ zawartość selenu w skorupie ziemskiej jest zróżnicowana w różnych miejscach, dodatek tego pierwiastka do karmy zwierząt jest wskazany celem uniknięcia chorób związanych z jego niedoborem. Ponadto suplementacja Se u bydła i owiec wiąże się ze zwiększoną produkcją embrionów, wysoką masą płodu i zmniejszoną częstością występowania zatrzymania łożyska. Jednak na pozytywne efekty diety wpływają inne czynniki środowiskowe, żywieniowe i związane z zarządzaniem, takie jak źródło selenu (organiczne lub nieorganiczne), czas i długość terapii, interakcja pierwiastków, skład diety. Potrzebne są dalsze badania mające na celu lepsze zrozumienie metabolizmu Se, szczególnie u przeżuwaczy, oraz wymagań dla optymalnego zdrowia. Związek między suplementacją Se i ryzykiem chorób reprodukcyjnych jest złożony, jednak wyniki ostatnich badań są obiecującym etapem na drodze do ustalenia dokładniejszych zaleceń dietetycznych zarówno dla ludzi, jak i dla zwierząt hodowlanych oraz opracowania efektywnych strategii prozdrowotnych.

Słowa kluczowe: selen, ciąża, łożysko, płód, ludzie, zwierzęta hodowlane.

INTRODUCTION

Selenium (Se) is an essential trace mineral for normal growth and development in livestock and humans, primarily known for its antioxidant, anti-inflammatory and antiviral properties (RAYMAN 2000, MCDOWELL 2003). Potential health benefits of supranutritional dietary Se in animals and humans include improved immune response and thyroid function, as well as cancer chemoprevention (use of natural or synthetic compounds to reverse, suppress or prevent cancer development) (CLARK et al. 1996, EL-BAYOUMY 2004, MICKE et al. 2005). Selenium's unique role in human physiology is also represented by the prevention of atherosclerosis, arthritis, diseases of accelerating aging, central nervous system pathologies and male infertility (Rayman 2000). Se deficiency in livestock leads to a nutritional myopathy (white muscle disease), ill thrift, infertility and impaired immunity (Van Metre, Callan 2001), while clinical cases are rare among humans (Burk, Levander 2006). In certain areas of China, Se deficiency predisposes patients to Keshan disease, an endemic viral cardiomyopathy primarily affecting children and young women (Koller, Exon 1986). In Siberian Russia and China, growing children with Se deficiency may develop chronic osteoarthropathy (Kaschin-beck disease) (Mo 1987). Since Se is required for the proper function of the immune system, it seems to be a key nutrient in counteracting the development of virulence and inhibiting HIV progression to AIDS (Rayman 2000). There is increasing evidence that Se supplementation of the maternal diet may be critical for progeny development and in humans a good Se nutrition has been suggested as an important factor for decreasing mortality and morbidity of preterm infants (Makhoul et al. 2004).

The present paper describes the results of numerous investigations into the effects of maternal Se supplementation on pregnancy and its role in normal placental and fetal development in both humans and livestock.

SELENIUM FUNCTION AND SUPPLEMENTATION

Se is an essential nutrient that exerts its biological functions as a component of at least three groups of proteins: glutathione peroxidase that is responsible for the reduction of hydroperoxides in cells, plasma and gastrointestinal tract; the iodothyronine deiodinases, responsible for the peripheral deiodination of thyroxin (T3) to 3,5,3 triiodothyronine (T2) and other metabolites; and thioredoxin reductases, which are involved in many cell functions, including control of apoptosis and maintenance of the cellular redox state (Rooke et al. 2004). Glutathione peroxidase, the most well-known selenoprotein (Sel), is an antioxidant enzyme protecting tissue against oxidative damage (Khan et al. 1995, Rayman 2000) and, therefore, Se plays an important role in scavenging free radicals, in regulating prokaryotic and eukaryotic cell survival and maintaining the integrity of intracellular organelles (Hostetler et al. 2003). This antioxidant function is shared with Vitamin E and, although both can be synergistically beneficial, animals at grass or with other green foods should be of adequate vitamin E status, while dietary Se deficiencies are both more frequent and severe so that Se supplementation is strictly recommended (Hemingway 2003). Se affects also cytochrome P450-dependent drug and xenobiotics metabolism (Shull et al. 1979) and counteracts the toxicity of several metals such as arsenic, cadmium, mercury and copper (Magos, Webb 1980). Moreover, Se plays a role in increasing intracellular killing by neutrophils (Gyang et al. 1984), antibody production and lymphocyte function in ruminants (Larsen et al. 1988). Unlike metals that interact with proteins in the form of cofactors, Se as a metalloid becomes cotranslationally incorporated into the polypeptide chain as part of the amino acid selenocysteine (Sec) and selenoproteins contain Sec as an integral part of their polypeptide chain (Pappas et al. 2008). Plants absorb Se from the soil in the form of selenite or selenate and synthesize selenomethionine (SeMet) (Rayman 2004). This means that Se in natural feed ingredients is mainly in the form of SeMet, which can also be synthesized by yeasts and some bacteria (Combs 2001). SeMet and Sec, the 21st amino acid (Böck et al. 1991), are identical to methionine and cysteine except for the sulphur (S) atom replaced by Se (Combs, Combs 1984). SeMet can be either reduced to form selenide or directly incorporated into proteins in place of Met (Butler et al. 1989). Vertebrates receive dietary Se in the forms of SeMet and other Se-amino acids (e.g. Se-methylselenocysteine, selenocystathionine) including Sec and its methylated forms, depending on their contents in food components. Although Se is widely distributed in the environment, Se content of food is greatly affected by the soil on which crops are grown or animals are grazed. Its concentrations and availability in soil in different countries are extremely variable and, specifically in Europe, the Se content of soil is low (McNeal, Balistrieri 1989). Therefore, currently, feeds for farm animals are supplemented with inorganic Se sources like sodium selenite (Na_2SeO_3) and sodium selenate (Na_2SeO_4) as well as with an organic form of Se, e.g. selenized yeast (Pappas et al. 2008) at concentrations that do not exceed 0.5 mg kg^{-1} (Commission Regulation EC 2006) and 0.3 mg kg^{-1} dm (FDA 2004) in Europe and USA, respectively. The dietary requirement of Se for both ruminants and non-ruminants is 0.1 mg kg^{-1} d.m. in the diet (Radostits et al. 2000), while the maximum tolerable level of Se has been increased from 2 (NRC 1980) to 5 mg kg^{-1} d.m. (NRC 2005). However, it has been stated that lower value are necessary to avoid excessive accumulation in edible tissues (NRC 2005). The main problems with excess Se are due to mixing errors or overdosing with injectable preparations. In these cases, the toxicity is acute and is manifested by poor growth, high Se content in tissues, abnormal gait, vomiting, dyspnea, titanic spasm, laboured respiration, and death (NRC 2005). “Blind staggers” has historically associated with subacute to chronic Se toxicity, even if it cannot be reproduced with pure Se compounds alone and likely involves other factors, such as alkaloid poisoning starvation, or polioencephalomalacia (Gupta 2007). Chronic selenosis causes depression, weakness, anemia, hair/wool loss, diarrhea, weight loss, lameness, hoof wall abnormalities and death (Gupta 2007). From first approval in 1974, either sodium selenate or sodium selenite could be used and, apparently, the two forms are of equal biopotency (Underwood, Suttle 2001). Indeed, it was found that, in the rat, 86% of a ^{75}Se-labeled oral dose of either sodium selenate or selenite is absorbed (Mason, Weaver 1986). However, when sodium selenite is orally given to ruminants, most of the Se is excreted in the feces (Cousins, Cairney 1961). Presumably, microorganisms and the reducing environment within the rumen promotes conversion of the selenite to less-soluble forms, such as elemental Se or selenides (Cousins, Cairney 1961). Furthermore, numerous studies have shown the retention of the selenomethione form, as found in selenium yeast, to be greater than the inorganic sources in tissue and blood (Pehrson et al. 1999). Thus, while the use of inorganic Se may prevent severe selenium deficiencies, supplementation with selenium yeast could provide enhanced Se status and antioxidant function at times of the greatest stresses and disease challenge, such as in the periparturient period (Wilde 2006). Se may be supplemented in livestock as a free-choice Se mineral supplement, fertilization, injection, oral drenching, distribution in water or ruminal pellets (Szarek et al. 1997). Alternatively, subcutaneous injection, usually as sodium selenite, or oral dosing with 10-30 mg of this compound for cattle and 1-5 mg for sheep are common means of preventing Se-responsive diseases in livestock. Heavy ruminal pellets, even in slow release bolus, prevent the occurrence of white muscle disease in sheep and cattle grazing Se-deficient pastures (Underwood, Suttle 2001). However, Se bioavailability and retention in ruminants is also influenced by diet composition, so that absorption of Se is greater in sheep receiving a concentrate-based diet than in sheep receiving a forage-based one (Koenig et al. 1997).

EFFECTS OF SELENIUM SUPPLEMENTATION ON PREGNANCY IN HUMANS AND LIVESTOCK

Selenium seems to be an integral element for normal reproductive function (Allison, Laven 2000). It is known that the incidence of retained placenta, abortion, early embryonic death and ovarian cysts increase in Se-deficient cows (Segerson et al. 1977, Maas 1983, Harrison et al. 1984, Vipond 1984, Cook, Green 2007) and that Se supplementation overcomes some forms of infertility in ewes (Hartley 1963). These beneficial effects can also be observed in avians, since the inclusion of Se in the maternal diet improves the embryo viability, hatchability and growth of the progeny (Pappas et al. 2006). In animal models, it has also been demonstrated that Se may modulate ovarian granulosa cell proliferation and estradiol-17β synthesis in vitro, affecting ovulation and the number of live embryos (Basini, Tamanini 2000). In humans, some studies have suggested that Se deficiency is related to adverse outcomes of pregnancy, miscarriages and preterm deliveries (Dobrzynski et al. 1998, Al-Kunani et al. 2001). In fact, both prenatal and postnatal Se supplementations are essential for proper functioning of antioxidant systems in offspring, already in place at the time of birth following prenatal supply and maintained after the first few days of progeny life by means of postnatal supplementation in maternal milk (Pappas et al. 2008). In man, several neonatal diseases (especially in preterm infants) are believed to be caused by oxygen free radicals, including bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus and hypoxic-ischemic encephalopathy (Gathwala, Yadav 2002). Se is transferred via the placenta and the mammary gland, with the action of SelP (selenoprotein P), which contains Se in the form of Sec (selenocysteine) and it is the major Se transporting system (Burk, Hill 2005). Both inorganic and organic Se regulate the expression of SelP, but it seems that the transport process – bi-directional in placental tissue – may be a more complex action than a simple passive transport mechanism (Korpela et al. 1984). Se in the colostrum is one of the selenoamino acids that are well tolerated by the progeny (Przybylska et al. 2007). The importance of Se in pregnancy has been demonstrated in humans, where women suffering from preeclampsia have reduced levels of Se in umbilical venous blood compared to normal pregnancy (Rayman et al. 2003, Mistry et al. 2008) and other studies have shown a decrease in maternal serum or toe-nail Se concentrations in preeclamptic patients (Rayman et al. 2003, Atamer et al. 2005). Preeclampsia is a systemic and serious complication of pregnancy that affects from 2% to 7% of all pregnancies, leading to maternal and perinatal mortality and morbidity both in the western world and developing countries and it is often associated with intrauterine growth retardation (IUGR) (Sibai et al. 2005). This disorder is characterized by hypertension, proteinuria, oedema and affects multiple organs, including the liver, kidney, brain and blood clotting system (Redman et al. 1999). Several lines of evidence support the oxidative hypothesis in the pathogenesis of preeclampsia, with placental underperfusion leading to an excessive production of reactive oxygen species and lipid peroxides causing oxidative stress and endothelial cell dysfunction (Hubel 1999). As expected, the activity of glutathione peroxidase is also decreased in preeclampsia as a function of Se depletion (Bulgan Kilicdag et al. 2005, Vanderlelie et al. 2005). Han and Zhou (1994) reports the beneficial effect of supplementation with 100 µg of Se per day in the prevention of pregnancy-induced hypertension and gestational oedema in a group of Chinese pregnant women. Moreover, Se supplementation in pregnant women effectively reduces the incidence of premature rupture of membranes (PROM) (Tara et al. 2010).

Similar findings have been reported in animals, although the effects of supplementation with Se on reproductive efficiency may be very variable (Hidiroglou 1979, Van metre, Callan 2001, Hemingway 2003, Rooke et al. 2004), probably as a result of variations in factors such as the source of Se, the period of supplementation before mating, and the Se and vitamin E status of the animals. Moreover, parenteral Se supplementation of pregnant ewes between 15-35 days after mating results in reduced embryonic survival rate, so that supplementation of ewes during the first month of pregnancy with parenteral Se preparations is not recommended (van niekerk et al. 1996).

Regarding the effect of Se supplementation on placental development, cotiledonary tissue appears to be more susceptible to a greater amount of Se than caruncular tissue (Lekatz et al. 2010a, 2010b). In fact, it has been demonstrated that there is an increased cellular proliferation and DNA concentration in cotiledonary tissue, but no effect on placentome number, mass and caruncular weight in supplemented ewes (LEKATS et al. 2010a). Interestingly, a high amount of Se does not decrease proliferation in placental tissue – as in certain types of cancer in humans (CLARK et al. 1996) – and the same finding occurs in the jejunal mucosa of pregnant ewes (NEVILLE et al. 2008) and beef steers (SOTO-NAVARRO et al. 2004). Both placenta and small intestine consume a large percentage of maintenance energy in ruminants (FERRELL, JENKINS 1985, REYNOLDS et al. 1990), but the mechanism by which Se increases cellular proliferation in these nutrient-transferring and metabolically important tissues is unknown. How Se alters proliferation in metabolically active tissue such as placenta is, however, largely dependent on timing and length of Se treatment since Se supplementation from 21 days before gestation until near term in ewes (days 135 of gestation), as aforementioned stated, increases cotiledonary cellular proliferation (LEKATZ et al. 2010b), while a supranutritional diet during mid- and late gestation decreases cell proliferation in the cotyledons (LEKATZ et al. 2010a). Furthermore, high dietary Se leads to greater glutathione peroxidase activity in cotiledonary and caruncular tissue than in normal levels fed to sheep (LEKATZ et al. 2010a). Se supplementation in ewes from 21 days before gestation until near term is also associated with increased Flt (VEGFR1) mRNA expression in cotiledonary tissue (LEKATZ et al. 2010b). Flt increases vascular permeability (PETERS et al. 1999), with following high fetal mass (LEKATZ et al. 2010b). In dairy cattle, supplementation with Se reduces the incidence of retained fetal membranes (RFM) (failure of expulsion of the placenta and associated membranes within 24h of calving) (ALLISON, LAVEN 2000, COOK, GREEN 2007) and cows with RFM have lower glutathione peroxidase activity in maternal and placental tissues than cows without retained placenta (KANKOFER et al. 1996). A study by HARRISON and CONRAD (1984) reported that animals supplemented with Se had no cases of RFM whereas the control animals have a 17% incidence. D'ALEO et al. (1983) reported similar results with control cows showing 20% incidence of RFM with a low Se diet against 0% among supplemented animals. Moreover, Se supplementation influences fetal development, as demonstrated by maternal supranutritional Se in ewes during mid- and late gestation that leads to increased fetal mass (REED et al. 2007, LEKATZ et al. 2010b, MEYER et al. 2010) and greater heart, lung, spleen, total viscera and large intestine weights compared to adequate supplemented foetuses (REED et al. 2007). Fetal muscle RNA concentration and heart RNA content are also higher after supplementation (REED et al. 2007). Furthermore, the effect of Se on fetal body mass is much more evident in ewes subjected to nutrient restriction (REED et al. 2007), suggesting that Se may provide a sparing effect on fetal body mass, despite the low amount of nutrients (GODFREY, BARKER 2000). In pigs, supplementation of pregnant sows with Se-Met also significantly increases the weaning litter weight and average piglets body mass (HU et al. 2010). Fetal tissue cellularity, especially in intestine, kidneys and liver, is responsive to maternal Se supplementation with selenate leading to a greater RNA : DNA ratio (index of cellular activity) in small intestine cells compared with High-Se wheat diet (Neville et al. 2008). These data also provide evidence of developmental programming of fetal internal organ cellularity in response to maternal Se supply (Neville et al. 2008). Regarding neonatal health and growth, Se supplementation of ewes' diet during early and mid-pregnancy, reduces the time taken for their lambs to stand and improves the immune status of the lambs, resulting in lower perinatal mortality and higher growth rates to weaning (Muńoz et al. 2009). Dietary Se intake seems to have an additional important effect on neonatal immune cell differentiation and function, since in neonates nursed by mothers fed a low-Se diet, the percentage of CD8 cytotoxic T cells, CD2 T cells, panB cells and natural killer cells are all decreased (Dylewski et al. 2002). Maternal and dietary Se may also influence antioxidant status in the testis of the offspring and the oxidative stress related to Se from the dam could modulate mRNA expression of apoptosis genes (Bcl-2, Bax and caspase-8) and programmed cell death of germ cells during spermatogenesis in the weaned kids (Shi et al. 2010).

In conclusion, the important effect of Se on animal and human reproduction underlines the role of dietary supplementation for increasing herd conception rates, lowering abortion cases in livestock and avoiding postnatal and prenatal feto-maternal disorders in humans. Nevertheless, the mechanisms of action of Se in many of these conditions are not fully known. In the context of ruminant production, data concerning the source and levels of selenium-rich feed are particularly important because of the rapid loading potential (Taylor 2005) and extended half-life of SeMet (Hawkes et al. 1994). SeMet-rich feed can be used to rapidly load animals and their foetuses or nursing offspring with Se before they are moved to remote Se-deficient ranges for an extended period of time. However, it should be taken into account that the variability in the herd response to supplementation may be due to a variety of dietary and management factors, including the concentration of interfering elements, the diet feeding pattern or the amount of concentrate which can affect the shrinking environment of the rumen, variations in soil characteristics and Se content between farms. In humans, providing antioxidants during pregnancy could decrease oxidative stress and may therefore prevent IUGR and preeclampsia. IUGR is a also major concern for the livestock industry because fetal growth restriction leads to negative impacts later in life on animal performance such as postnatal growth, body composition and reproductive performance.

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