Maternal Selenium and Developmental Programming

Subjects: Medicine, General & Internal

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Selenium (Se) is an essential trace element of fundamental importance to health due to its antioxidant, anti-inflammatory, and chemopreventive properties, attributed to its presence within at least 25 selenoproteins (Sel).

Keywords: embryonic development ; maternal nutrition ; periconceptional period ; progeny ; selenium ; selenoproteins

1. Introduction

Maternal nutrition is of critical importance for fetal growth. An unbalanced nutrient supply will result in low birthweight and, subsequently, compromise future growth and development. Apart from short-term outcomes, accumulating evidence from animal and human studies indicates that early life experiences can impact offspring phenotype, a concept known as Developmental Origins of Health and Disease (DOHaD) hypothesis [1]. Variation in the maternal plane of nutrition, and particularly maternal under or over nutrition, appears to be a dominant factor in developmental programming, in both humans and livestock, including metabolic [2], productive [3][4], and reproductive outcomes [5][6]. In addition, maternal nutritional imbalances in terms of both macro and micro nutrients can induce oxidative stress, which may affect fetal growth and development [7]. Recently, the role of colostrum in affecting the critical developmental process, as a conduit of transmission of certain bioactive molecules from mother to offspring, has attracted considerable attention, according to lactocrine signaling hypothesis [8]. The periconceptional period is playing a crucial role in programming effects, since it is characterized by extensive reorganization of cellular phenotype during oocyte maturation, fertilization, and embryonic genome activation [9]. Even in poultry species, the prenatal environment can be divided into pre-lay and egg storage/incubation environments, both of which can affect offspring outcomes. In particular, maternal nutrition is of paramount importance because all nutrients required by the developing embryo are deposited in the egg and therefore exert an effect not only during embryonic but also during posthatch development [10].

Apart from the well-established role of micronutrients in short-term pregnancy outcomes [11], accumulating evidence also supports a role for micronutrients in developmental programming [12][13][14]. Trace elements affect the endocrine regulation of energy metabolism and energy homeostasis, as well as oxidative balance, both of which are related to normal growth [15]. In particular, Se possesses antioxidant, chemopreventive, and anti-inflammatory properties and is considered as a trace element of great importance to the health of both mammals and avian species. Its action is related to its presence within at least 25 selenoproteins, i.e., Se-containing proteins products of twenty-five genes. Among them some are well characterized with respect to their function like the glutathione peroxidases (GPX1, GPX2, GPX3, GPX4, and GPX 6), the thioredoxin reductases (TXNRD1, TXNRD2, and TXNRD3), and the iodothyronine deiodinases (DIO1, DIO2, and DIO3). Other selenoproteins include but are not limited to selenophosphate synthetase 2 (SEPHS2), selenoprotein F or selenoprotein 15 (SELENOF), selenoprotein H (SELENOH), selenoprotein I (SELENOI), selenoprotein K (SELENOK), selenoprotein M (SELENOM), selenoprotein N (SELENON), selenoprotein O (SELENOO), selenoprotein P (SELENOP), selenoprotein S (SELENOS), selenoprotein T (SELENOT), selenoprotein V (SELENOV), and selenoprotein W (SELENOW) [16][17]. Selenoprotein P is the major Se transporting protein [18], and is considered the only known protein that contains multiple selenocysteine residues per protein molecule [19].

Selenomethionine and selenocysteine are identical to methionine and cysteine, respectively, except that the sulphur atom is replaced by Se. Plants synthesize selenomethionine and a variety of methylated amino acids. Plants absorb Se from the soil in the form of selenite or selenate and synthesize selenomethionine [20][21]. In feed ingredients, Se can be found in form of selenomethionine. In addition, to the amount of Se received from feed ingredients, feeds of farm animals are widely supplemented. Selenium is generally supplemented in the form of inorganic Se or in organic form, and the most widely used sources include sodium selenite, sodium selenate, controlled-release sodium selenite bolus, SeMet, zinc L-selenomethionine complex, hydroxy-analogue of selenomethionine, Se-yeast, elemental Se at nano size, soybean Se proteinate, Se-enriched malt, chlorella algae, cabbage, and garlic [22][23][24][25]. Selenium efficiency depends on the level of supplementation and form of Se in the diet, and organic sources proven to be effective sources of Se for poultry and

animal production [26][27]. In EU, the maximum supplementation with organic Se is 0.2 mg Se per kg of complete feed, while the maximum content of Se (total Se) is 0.5 mg/kg of complete feed [28]. Similarly, the Food and Drug Administration (FDA) regulations limit the amount of dietary Se supplementation, to 0.3 mg/kg (as fed) [29]. Given the FDA limits, any concentration that exceeds 0.3 mg/kg and is below the maximum tolerable level can be considered as supranutritional.

Recently, the role of Se in maternal nutrition and its impact on the Se status of offspring has received considerable attention. In mammals, Se is transferred both via the placenta, the colostrum, and milk to the fetus and the neonate [30]. In avian species, laying hen transfers Se to the egg and in turn to the developing embryo and newly hatched chick [10][31][32]. Selenium affects non-enzymatic and enzymatic antioxidant defense mechanisms, helping build a strong antioxidant defense for both mother and the developing embryo. Recent studies in humans have also revealed an association between maternal Se status and specific early childhood outcomes. Both low and high levels of cord serum Se have adverse effects on an infant's neurobehavioral development [33]. More interestingly, a positive effect of maternal selenium status on children's development at 1.5 years of age has been reported, related to language and psychomotor development improvement [34]. These findings have been supported by data from human cohort studies. In particular, in a Polish cohort study involving 410 mother-child pairs, a significant positive association was detected between Se levels in the blood collected during the first trimester of pregnancy and child motor skills at 1 and 2 years of age and cognitive development at 2 years of age [35].

2. Combined Effects of Maternal Plane of Nutrition and Selenium Status on Progeny

Numerous studies have investigated the interaction between maternal plane of nutrition and Se status on a number of physiological parameters in the offspring. In particular, inconsistent results of the effects of maternal supranutritional Se supplementation regarding birth weight or weight at weaning have been reported in sheep ranging from no effect [36] to an increase in birth weight and weight at weaning, regardless of global maternal nutrient intakes [37][38]. On the other hand, supranutritional Se supplementation to nutritionally restricted dams (60% of their needs) resulted in improved fetal growth, implicating a sparing effect of Se and long-term developmental consequences [37][38].

In pigs, maternal supplementation with SeMet significantly increases litter weight at weaning and body mass of piglets [39], whereas in chickens, inclusion of Se in the maternal diet could positively affect embryo viability, hatchability, and growth of the progeny [10][31][32]. In the same species, dietary inclusion of organic Se (zinc L-selenomethionine complex) promoted heavier hatchling weight until egg production peak, (33 week), without affecting hatchling quality [40]. Moreover, supplementation of the breeder's diet with organo-Se appears to enhance the DHA concentration of the chick brain [10], in good agreement with the well accepted role of Se in protecting polyunsaturated fatty acids (PUFA) oxidation [41].

In large animals, the majority of the studies examining the role of Se in modifying the effects of nutrition are mostly limited to the late gestation fetus, and only a few examine later outcomes. Six-months old lambs, derived from ewes supplemented with supranutritional Se and artificially reared to avoid confounding effects with colostral Se, showed greater small intestinal weight, which, however, was not accompanied by an increase in jejunal cell proliferation [42]. As is pointed out by authors, this increase could be translated to increased crypt cell proliferation and altered villi number, leading probably to more efficient nutrient absorption.

It has been well documented that maternal nutritional status impacts mammary gland development and, subsequently, colostrum and milk yield [36][43]. However, data from primiparous ewes indicate that supranutritional supplementation from conception to term may be a more potent factor in driving milk production [43]. Interestingly, Se supplementation in ewes at approximately 10 times above current recommendations was reported to increase mammary gland capillary area density and vascularity, a finding explaining the increase in milk production, possibly by enhancing the nutrient availability to the mammary gland [44].

Recently, the role of Se in metabolic programming has gained interest [45]. This micronutrient, through the activity of selenoproteins, such as glutathione peroxidase and selenoprotein P, has been reported to play a role in the regulation of enzymes in the insulin signaling cascade, the expression of lipogenic enzymes, and carbohydrate metabolism in the liver [46][47][48]. In this respect, studies in sheep revealed an interaction between nutritional and Se maternal status on insulin sensitivity in offspring. Lambs born to high-Se but restricted-diet mothers exhibit an elevated insulin release following intravenous glucose tolerance test [37]. Moreover, the same offspring were characterized by greater total visceral adiposity, attributed mainly to an increase in visceral rather than omental fat [37]. The involvement of Se and its selenoproteins, glutathione peroxidase and selenoprotein P, in insulin regulation has been confirmed from a number of studies, indicating a role in insulin signaling cascade [48][49]. However, recent evidence indicates that effects are related to the level of

supplementation. Adequate concentrations exert a key role in insulin function, but an excess is associated with insulin resistance [50]. The underlying mechanism probably involves formation of antioxidant selenoproteins and thus reduced concentrations of reactive oxygen species, which are required for insulin signaling [51][52]. Therefore, the exact impact of maternal Se and especially the level of supplementation in insulin-glucose axis regulation in the offspring is not yet clear and needs further elucidation. A summary of selected animal studies reporting combined effects of maternal plane of nutrition and Se status on progeny is presented in **Table 1**.

Table 1. A summary of selected studies describing the combined effects of maternal plane of nutrition and selenium status on progeny.

Animal Model	Study Design	Key Findings as Reported by Authors	Reference
Broiler breeders/broilers	Low (0.1 mg/kg) or High (0.5 mg/kg) selenium (Se) status (Se yeast) and soyabean oil and low or high (0.5 mg/kg) Se status and fish oil and progeny fed high or low (20% less energy and protein) diets with similar Se content	Broilers fed for two weeks posthatch a diet with similar Se content but hatched from parents fed high-Se diets had higher tissue Se concentrations than those hatched from parents fed diets low in Se Supplementation of the maternal diet of chicks with organo Se compounds enhanced the concentration of docosahexaenoic acid in the brain of progeny	[10]
Broiler breeders/broilers	Vitamin E at two levels (30, 120 mg/kg) and two sources of Se (Sodium selenite or Zinc-L-SeMet) at 0.4 mg/kg	Inclusion of organic selenium in breeders diet led to heavier hatchling weight until egg production peak (33 wk) Hatchability of the eggs from 29 wk old breeders fed 120 mg vitamin E/kg feed was higher than that of breeders fed 30 mg vitamin E	[40]
Ewes/lambs	Adequate (9.5 µg/kg body weight (BW)) or High (81.8 µg/kg BW) and nutritional status 60% of metabolisable energy requirements (Restricted), 100% (Control), and 140% (High)	Female lambs from high Se ewes were heavier at birth Maternal Se intake can enhance fat deposition in female offspring Nutritional intake × Se status interaction on growth rate of lambs and insulin response on a glucose tolerance test; thus, both maternal nutritional level and Se intake can influence insulin sensitivity	[37]
Ewes/lambs	Adequate (9.5 µg/kg BW) or High (81.8 µg/kg BW) and nutritional status 60% of metabolisable energy requirements (Restricted), 100% (Control), and 140% (High)	High maternal Se led to greater jejunal capillary area density in the offspring	[42]
Ewes/lambs	Adequate (9.5 µg/kg BW) or High (81.8 µg/kg BW) and nutritional status 60% of metabolisable energy requirements (Restricted), 100% (Control), and 140% (High)	Colostrum and milk yield greater in high- vs. adequate-Se-fed ewes	[43]
Ewes/lambs	Adequate (9.5 µg/kg BW) or High (81.8 µg/kg BW) and nutritional status 60% of metabolisable energy requirements (Restricted), 100% (Control), and 140% (High)	Progeny from high-Se ewes had greater capillary surface density compared with those from adequate group	[44]
Sows/piglets	0.042 mg/kg or 0.3 mg/kg as sodium selenite or selenomethionine	Maternal selenomethionine vs. inorganic Se significantly increased the weaning litter weight and average weight of piglets	[39]
Dam rats/pups	0.01 mg Se/kg diet (deficient-low), 0.1 mg /kg, and 0.5 mg Se/kg diet (supplemented-high)	Pups born from mothers fed excess Se exhibited insulin resistance	[50]

3. Effects of Maternal Selenium Status on Reproduction of the Offspring

The reproductive axis and its hormonal control systems are largely established during fetal life, representing a target for developmental programming [53][54]. Accumulating evidence supports a crucial role of Se for fetal reproductive organ development in both sexes, probably mediated by its antioxidant properties. In particular, the testis represents a specific target for Se function, as being crucial for normal spermatogenesis and maintenance of male fertility [55].

Recent data from a number of studies in male goat offspring support a role of maternal Se status in the development of testis and spermatogenesis after weaning. Supplementation of maternal diet with Se (as Se enriched yeast) at different

levels (0, 0.5, 2.0, and 4.0 mg/kg) improved the testosterone level and promoted the expression of testosterone related genes, in offspring testis, which, however, was decreasing as Se supplementation was increased [56]. Moreover, offspring exhibited different expression profile for a number of germ cycle-related genes in their testis, depending on the different supplementation levels. In particular, it was shown that both maternal Se deficiency and excess could prevent the completion of cell cycle and induce an increase in the apoptotic rate of germ cells [57]. These data indicate that supplementation of maternal diet during gestation could provide the Se necessary for normal development of reproductive function of the offspring, but on the other hand, underline the importance of determining the necessary level of supplementation, as Se excess leads to opposite effects.

Regarding female organ development, Grazul Bilska et al. [58] reported that maternal Se dietary intake may be involved in the regulation of early folliculogenesis and cellular proliferation of the follicles, blood vessels, and stromal tissues of fetal ovaries in sheep. In support of these findings, in vitro studies with bovine granulosa cells revealed a positive action of Se in promoting granulosa cell proliferation and E2 production, an effect possibly mediated through decreased NO production caused by Se [59].

In avian species, similar to mammals, reproduction outcome is greatly affected by the quality of the semen of the male. Avian semen is rich in PUFA and thus susceptible to lipid peroxidation. In detail, phospholipids of chicken spermatozoa are rich in long-chain fatty acids of the n-6 family, most notably arachidonic (20:4n−6) and docosatetraenoic (22:4n−6) acids [60]. In duck, spermatozoa contain a much higher proportion of docosahexaenoic acid (22:6n-3) in the sperm lipids [61], indicating the susceptibility to peroxidation. Optimal Se status of parent stock (breeders) can maintain the semen quality and provide the antioxidant environment for the developing embryo [26]. In this context, the average Se concentration in the semen of chickens fed a non-supplemented diet (0.1 mg/kg) was shown to be 47 ± 3 ng/g, while in breeders fed a Se supplemented diet (0.5 mg/kg) it was shown to be 101 ± 10 ng/g [62]. Regarding the link between female reproduction and Se, a preliminary study on broiler breeders established a positive relationship between Se addition and gene transcription [63]. In detail, Se was associated with genes encoding energy-associated mitochondrial proteins and protein synthesis networks, indicating that Se, especially in the organic form, is necessary for optimal energy production and protein translation in female reproductive tissues [63]. Yuan et al. [64] reported little influence on the egg production rate and fertilization rate of broiler breeders fed Se from different sources. However, organic Se sources at 0.3 ppm resulted in greater deposition of Se in breeders, egg, embryo, and offspring chicks compared to inorganic Se. The same authors reported that among organic Se sources, SeMet had higher tissue Se retention than Se yeast, indicating that maternal effects may be more pronounced when broiler breeders are fed with SeMet [64].

One of the significant gaps regarding the role of maternal Se on reproductive health is the identification of the best timing of supplementation. Recently, the periconceptional period has attracted more attention in the context of developmental programming concept, being the potentially more critical period in which developmental plasticity is vulnerable to environmental challenges, including maternal macro and micro nutrition. This period encompasses gametogenesis, fertilization, conceptus formation, implantation, and placentation, which represent particular time windows during which epigenetic changes can have long-lasting consequences on the development and function of the tissues and therefore long-term effects on offspring phenotype [65]. An experiment in mice, involving Se supplementation during three different stages of periconception period, revealed that the pregestation and gestation periods are optimal developmental windows of Se supplementation for improved quality of blastocysts and reduced preimplantation loss [66].

It is well acknowledged that gametes and embryos function better when the redox potential is higher, but on the other hand it must be kept in mind that excess supplementation of antioxidants may suppress the beneficial signaling function of reactive oxygen species and impair their reproductive potential [67].

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