Selenium in reproductive health

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Selenium was first discovered in 1817 by Jöns Jacob Berzelius when investigating the chemicals responsible for outbreaks of ill health among workers in a Swedish sulphuric acid plant. The local product contained a contaminant that he named Selén, after the Greek goddess of the moon. In 1957, Klaus Schwarz with Foltz proved that selenium is an essential nutrient necessary for both normal growth and reproduction in animals.

Selenium, amino acids, and selenoproteins
Dietary selenium, initially taken up from the soil and concentrated by plants, is absorbed in the small intestine and incorporated into proteins by complex mechanisms that remain unclear. Selenite (SeO\textsubscript{3}\textsuperscript{2-}; inorganic form of selenium) crosses the plasma membrane and reacts with cytoplasmic thiols in the reduction pathway; this forms selenide, which is then methylated, giving rise to methylated selenide derivatives that are excreted in urine, expired air via the lungs, and feces (Figure 1). The proportion of selenium intake excreted like this depends on dietary intakes; when this is high, urinary excretion will also be high and vice versa.

Selenium is stored in the tissues in varying density: 30% in the liver, 30% in muscle, 15% in the kidney, 10% in the plasma, and the remaining 15% throughout other organs. Concentrations of free selenium are greatest in the renal cortex and pituitary gland, followed by the thyroid gland, adrenals, testes, ovaries, liver, spleen, and cerebral cortex.

Selenium concentrations are typically measured in plasma, serum, whole blood, amniotic fluid, and urine as well as hair and toenails (reflecting longer-term selenium stores). The main methods used to be atomic absorption spectrometry; however, more recently inductively coupled plasma-mass spectrometry has been used, which has improved the limits of detection to 0.055 μg/L.

Selenoproteins, coded by 25 selenoprotein genes in humans (Table 1), exert multiple actions on endocrine, immune, and inflammatory functions. Of particular importance to reproduction and pregnancy are the 6 antioxidant glutathione peroxidases (GPxs), which play a pivotal role in reducing hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) and lipid peroxides to harmless products (water and alcohols; Figure 2), thereby dampening the propagation of damaging reactive oxygen species (ROS). As antioxidants, the GPxs help maintain membrane integrity, protect prostacyclin production, and limit the propagation of oxidative damage to lipids, lipoproteins, and deoxyribonucleic acid (DNA).

Dietary selenium
Plant foods are the major dietary sources of selenium in most countries. Wheat is the most efficient selenium accumulator of the common cereals and is 1 of the most important selenium sources for man. The content in food depends on the selenium content of the soil in which plants are grown or animals are raised. For example, the selenium content in the soil of the high plains of northern Nebraska and the Dakotas is very high, and the inhabitants have the highest selenium intakes in the United States. Other foods make a substantial contribution to selenium intake in northern Europe, particularly meat, poultry, and fish (a total of about 36% in...
Selenide (CH₃SeH), dimethylselenide ([CH₃]₂Se), trimethylselenonium ion ((CH₃)₃Se⁺) leaches selenium from the soil.²⁰,²⁴ Selenium incorporation into plants, and then into animal tissues, depends on not only soil selenium content or geochemistry but also soil pH, rainfall, land contour, and the use of high-sulphur fertilizers. Some bacteria can convert insoluble forms of selenium to soluble forms, which can then be taken up by plants.²⁰,²⁴

Selenium toxicity

There is also a moderate to high health risk of selenium toxicity, first discovered in animals grazing in areas with high selenium content in the soil.³⁸ Chronic toxicity of selenium in humans results in selenosis, a condition characterized by brittleness or loss of hair and nails, gastrointestinal problems, rashes, garlicky breath odor, and nervous system abnormalities.³⁹ In China, it has been reported that selenosis occurs with increased frequency in people who consumed selenium at levels above 850 μg/d.⁴⁰ The Institute of Medicine (United States) has set a tolerable upper intake level for selenium at 400 μg/d for adults to prevent the risk of developing selenosis.⁴¹ The European Commission and the World Health Organization have proposed the lower daily intake in most parts of Europe is considerably lower than in the United States, mainly because of the European soils providing a poorer source of selenium.¹⁵,³⁰

Assessments of requirements, adequacy, and intakes of selenium have been reviewed previously in detail¹⁵,³⁰ and summarized in Table 2. Selenium intake appears on average to be at or above the recommended dietary intakes in the United States (60-220 μg/d)¹⁹,³¹,³² or Canada (50-200 μg/d).³⁵,³⁴ However, modest selenium deficiency, in association with poor diet, has been described in the United States among the poor and obese, which a recent review links prospectively to cardiovascular disease and immune dysfunction.³⁵ In the United Kingdom, selenium dietary intake is generally below the reference nutrient intakes (30-40 μg/d).²²,³⁶,³⁷

Selenium in reproductive health

Male fertility

Selenium is essential for testosterone biosynthesis and the formation and normal development of spermatozoa.⁴⁴,⁴⁵ Testicular tissue contains high concentrations of selenium, predominantly as GPx4, and this provides the link between selenium, sperm quality, and male fertil-
ity because GPx4 is a fundamental determinant of the architecture of the spermatozoan midpiece, and is considered to shield developing sperm cells from oxidative DNA damage. ROS have been implicated in male infertility because, through attack of the spermatozoan membrane, sperm viability is decreased.

Some evidence suggests that increasing selenium dietary intake increases antioxidant GPx activity, thereby increasing male fertility. The study in 1984 by Bleau et al. reported an optimal range between 50 and 60 μg/mL in semen and a positive correlation between sperm count and semen selenium concentration in 125 men from couples being investigated for infertility.

In Scotland, a placebo-controlled randomized control trial (RCT) of 64 men demonstrated that sperm quality and fertility improved after selenium supplementation. Other placebo-controlled RCTs from Tunisia and Iran of infertile men demonstrated the beneficial effects of daily supplements of selenium on improving sperm motility, semen quality including sperm count, concentration, morphology, and motility as well as plasma and semen selenium concentrations.

A recent study of 690 infertile Iranian men with idiopathic asthenoteratospermia who received supplemental daily selenium (200 μg) in combination with vitamin E (400 U) for at least 100 days observed a 52.6% total improvement in sperm characteristics (362 cases), and 10.8% spontaneous pregnancies in comparison with no treatment (95% confidence interval, 3.08–5.52). However, this study was not a placebo-controlled blinded RCT.

Some studies have reported contrary results in relation to selenium supplementation. Three small studies, from Poland and the United States, supplementing (200–300 mg/d) with selenite, selenium-enriched yeast, or diets naturally high in selenium reported that, although semen selenium concentrations increased, there were no positive effects on sperm characteristics or activity. Indeed, 1 reported decreased sperm motility. These studies highlight that the dosage of supplementation needs to be carefully considered, especially studies such as these, in which basic selenium intake, as in the United States is generally higher.

Another point to note is that the participants in 2 of these studies were healthy men with no fertility problems, so selenium supplementation may not have had any effect. A recent review of the effect of oral antioxidants (including selenium) on male subfertility concluded that supplementation could improve sperm quality and/or pregnancy rates but recommended that large adequately powered trials using individual antioxidants are required.

### Female fertility

Data regarding selenium and female fertility are sparse. Paszkowski et al. completed a study of 135 follicular fluid samples collected from 115 patients during transvaginal oocyte retrieval; patients with unexplained infertility had significantly decreased follicular selenium concentrations compared with those with tubal infertility or a known male-related cause of infertility. A recent case-controlled study from Turkey also found lower serum and follicular fluid selenium concentrations in 30 women undergoing in vitro fertilization treatment compared with 13 age-matched, nonpregnant control women. Women with unexplained infertility or premature ovarian failure have significantly increased serum levels of the ovarian autoantibody protein, selenium-binding protein-1.
Super oxide can be generated by specialized enzymes, such as the xanthine or nicotinamide adenine dinucleotide phosphate oxidase (NADPH) oxidases or as a byproduct of cellular metabolism, particularly the mitochondrial electron transport chain. Superoxide dismutase (SOD) then converts the superoxide \( \left( O_2^- \right) \) to hydrogen peroxide \( \left( H_2O_2 \right) \), which has to be rapidly removed from the system. This is generally achieved by catalase or peroxidases, such as the selenium-dependent GPxs, which use reduced glutathione (GSH) as the electron donor.

GSSG, glutathione disulfide.


### Selenium and disorders of pregnancy

#### Miscarriage

Miscarriage, a clinically detectable pregnancy that fails to progress past 24 weeks’ gestation, occurs in 10-20% of all pregnancies. Genetic (chromosomal) abnormalities explain at least half of all miscarriages. Although anatomical, endocrine, immune, infective, and thrombophilic conditions are other possible causes, most chromosomally normal miscarriages remain unexplained or idiopathic.

In humans, a UK observational study reported significantly lower serum selenium concentrations in 40 women with first-trimester miscarriage compared with 40 age-matched nonpregnant and 40 healthy gestation-matched women; a similar finding was reported in another observational study from Turkey.

Red-cell and hair selenium concentrations are also reported to be lower in women with recurrent miscarriage. Conversely, a retrospective case-control study of nonpregnant women found no differences in selenium concentration in 47 women with a history of recurrent miscarriage compared with 47 controls. It must be noted that unlike the aforementioned studies, which were women in early pregnancy, selenium concentrations in men and women in the reproductive age groups were significantly higher in those who reported reproductive abnormalities compared with normotensive populations.
pregnancy, these were nonpregnant, and no information on parity or interpregnancy intervals are provided, which could confound the results. Early pregnancy loss has been linked to reduced antioxidant protection of biological membranes and DNA and also to low concentrations of the GPx, warranting further investigations to establish whether women with recurrent pregnancy loss could potentially benefit from the optimization of selenium status.

**Preeclampsia**

Preeclampsia (de novo proteinuric hypertension) is estimated to occur in approximately 3% of all pregnancies and is a leading cause of maternal and perinatal mortality and morbidity in the Western world; together with other hypertensive disorders of pregnancy, preeclampsia is responsible for approximately 60,000 maternal deaths each year and increases perinatal mortality 5-fold. Placental and maternal systemic oxidative stress are components of the syndrome and contribute to a generalized maternal systemic inflammatory activation. Placental ischemia-reperfusion injury has been implicated in excessive production of ROS, causing release of placental factors that mediate the inflammatory responses.

In light of the association between oxidative stress and the prevalence of low dietary selenium status worldwide, several studies have suggested that selenium deficiency may be linked to preeclampsia. The recent appreciation that nutrient-gene interactions may play a major role in manifestation of hereditary disease traits could be of relevance to the association between selenium status and preeclampsia.

Several genes that encode selenoproteins demonstrate functional polymorphisms. Examples include GPx3, functional polymorphisms that decrease transcriptional activation, gene expression, and plasma protein activities. A single nucleotide polymorphism within the 3’ untranslated region of the GPx4 gene (GPx4c718t) affects GPx protein concentration and activity but also has differential effects on GPx3 and GPx1 when selenium supplementation is stopped, although this needs to be investigated in relation to preeclampsia.

Selenoprotein S (also known as SEPS1 or VIMP), which contains a Sec residue at its active site, is an antiinflammatory protein that acts primarily to limit the damaging consequences of endoplasmic reticulum stress. It has recently been suggested to contribute to the development of preeclampsia. A polymorphic variant in the SEPS1 locus has been associated with increased cardiovascular disease morbidity in Finnish females and a 105G>A promoter polymorphism associated with reduced function has been defined and is significantly but not strongly associated with preeclampsia.

Preeclampsia has a familial component. A high prevalence of these polymorphisms could, together with selenium deficiency, be a major determinant of impaired antioxidant defense in this disorder, through altered selenoprotein activity, and thereby contribute to development of the disease through nutrientomic pathways.

In the United Kingdom, where selenium dietary intake is low, our group and others have reported selenium concentrations in preeclamptic pregnancies to be reduced in sera from the mother, and fetus as well as in amniotic fluid and in toenails when compared with normal pregnant controls. Conversely, others have shown no differences, and in 1 study from the United States, higher sera selenium concentrations have been reported in women with preeclampsia. However, a reported lack of sensitivity of the assays used, or dependence of the maternal leucocyte selenium content in estimation of selenium status, may confound the interpretation of these studies.

GPx activities in both maternal and cord plasma have also been shown to be lower in preeclamptic pregnancies. Several retrospective studies from Turkey, the United States, and Australia of maternal plasma or placental tissue collected from normal pregnancy and preeclampsia report a reduction in GPx activity in preeclampsia. Our group recently conducted a retrospective cross-sectional study in the United Kingdom of 25 preeclamptic women and 27 healthy controls as well as cord blood and placental tissue collected immediately after delivery. Total GPx activity in plasma and in placental tissue were significantly reduced in preeclampsia. Further prospective, longitudinal studies are required to elucidate a cause-or-effect relationship.

If selenium deficiency is confirmed in women suffering from preeclampsia and this continues to be linked with GPx inadequacy, adequately powered selenium supplementation trials in pregnancy may be of benefit in prevention or amelioration of preeclampsia.

Some small studies have attempted to assess the influence of selenium supplementation on the incidence of pregnancy-related hypertensive disorders. Beijing has a high incidence of both selenium deficiency and pregnancy-induced hypertension (PIH). One hundred women with known risk factors for PIH were randomized to selenium (100 μg/d) or placebo for 6–8 weeks during late pregnancy. Maternal and umbilical serum selenium rose significantly, and the incidence of PIH reportedly decreased. Another very small, prospective, double-blind, placebo-controlled RCT in Indonesia also reported lower rates of preeclampsia and/or PIH in women who were at increased risk of developing these conditions after supplementation with a range of antioxidants and cofactors including selenium (100 μg). Neither study adequately addressed the role of supplementation on the incidence of preeclampsia.

Recently, however, Tara et al investigated selenium supplementation of Iranian women in their first trimester (100 μg selenium per day) in a small pilot RCT and concluded that supplementation may be associated with a lower frequency of preeclampsia, although this just failed to reach statistical significance.

There is no current consensus on the optimal dietary selenium supplement for use in clinical supplementation because bioavailability and effects on expression of the various selenoproteins depend on the form of selenium product used. A small UK-based RCT of selenium supplementation (selenium in pregnancy; Systolic Blood Pressure Intervention Trial) is ongoing. Although not powered to demonstrate clinical benefit, this study is designed to assess
the impact of selenium supplements on preeclampsia-related biomarkers. If successful, a larger multicenter RCT adequately powered to detect differences in the rates of preeclampsia will be needed to assess the potential clinical benefit.

**Preterm labor**

Preterm labor (labor <37 weeks’ gestation) is a major cause of perinatal morbidity and mortality occurring in 6-7% pregnancies in the developed world and up to 25% in undeveloped countries and is likely to be of complex origin. A few studies have investigated selenium and preterm labor. Cross-sectional studies in India, Holland, Germany, and Iran all reported lower plasma selenium concentrations in women delivering preterm as compared with women delivering at term.

Another study from Poland reported lower maternal selenium concentrations and reduced maternal and cord plasma GPx activities in 46 women who delivered preterm compared with 42 women delivering at term. The low selenium concentrations and GPx activities in the blood of the preterm infants may contribute to their susceptibility to sepsis and other prematurity-related conditions. A study from the United States of 13 preterm and 15 term infants also reported that preterm infants had lower selenium concentrations compared with term infants, although maternal concentrations were not significantly different. As might be anticipated, the daily dietary selenium intake was 2-3 times higher (96-134 μg) than in the subjects reported in the Polish population. Population selenium intake may explain some variation between studies.

Preterm premature rupture of membranes before the onset of labor (PPROM) is a major initiating factor in preterm labor and affects 10-12% of all pregnancies. PPROM is associated worldwide with increased rates of neonatal and maternal morbidity and mortality. Increased generation of ROS as well as antioxidant deficiency may play an important role in the pathophysiology of PPROM, which has been associated with enhancement of collagen degradation and subsequent damage to fetal membrane integrity.

A potential association with selenium has been highlighted through a recent small, prospective, double blind, placebo-controlled RCT in Iran, which randomized 166 primigravid pregnant women in the first trimester of pregnancy to receive 100 μg/d selenium or placebo until delivery. The supplemented group demonstrated a significant increase in the mean serum selenium concentration and a reduction in the incidence of PPROM.123

**Small for gestation age**

A small-for-gestational-age (SGA) infant is defined as an individualized birthweight ratio below the 10th percentile and is associated with increased perinatal mortality and morbidity. A recent paper from North Dakota State University suggests some protective effect of high selenium intake in nutrient-restricted pregnant ewes on fetal birthweight and placental development. Some studies of SGA deliveries report reduced placental selenium concentrations, whereas others report higher or unchanged concentrations. Strambi et al demonstrated that in 81 SGA (both term and preterm) retrospective subjects from Italy, infant plasma selenium concentrations were significantly lower compared with adequate-for-gestational-age (AGA) infants.

A recent investigation by our group in a cohort of poor adolescent pregnant women from 2 UK inner cities found lower plasma selenium concentrations in mothers who delivered SGA infants compared with mothers who delivered AGA infants. Again, geographical differences may explain the difference between the selenium status in the different studies. We are not aware of any ongoing studies investigating maternal and fetal selenium status in relation to fetal growth restriction.

**Obstetric cholestasis**

Obstetric cholestasis (OC) is a serious complication of pregnancy and affects approximately 4500 women per year in the United Kingdom. Affected women develop itching, otherwise-unexplained elevation of plasma liver enzymes and serum bile acids and occasionally jaundice. OC is associated with an increased risk of premature delivery and fetal distress and is believed to be an important cause of stillbirth. Kauppila et al demonstrated in 1987 that serum selenium concentrations and GPx activities were significantly lower in 12 Finnish women with OC when compared with 12 normal pregnancies during the last trimester and postpartum. These initial results were confirmed and extended in a study in Chile, also showing that the decrease in prevalence of OC in Chile during the last decade coincided with an increase in plasma selenium concentrations.

Thus, it has been hypothesized that inadequate antioxidant protection may lead to hepatocyte oxidative damage and reduce excretion of bile.

**Gestational diabetes mellitus**

Gestational diabetes mellitus (GDM) is one of the commonest diseases in pregnancy and is an increasing problem with an incidence of 7.6%. GDM is defined as a deficient insulin supply relative to the increased demands that are characteristic of pregnancy. GDM is associated with birthweight above the 90th centile, increased levels of primary cesarean deliveries, and neonatal hypoglycemia if left untreated or undiagnosed. The causes are not known but are closely related to a constitutional risk of type 2 diabetes in later life and strongly associated with obesity.

In diabetes protein glycosylation and glucose autooxidation can lead to the formation of free radicals, possibly inducing lipid peroxidation. An important factor responsible for the development of oxidative stress and ROS is hyperglycemia that occurs in diabetic pregnancy.

Several studies from China, Kuwait, Turkey, and the United States have shown a decrease in maternal plasma selenium concentrations in women with GDM. Bo et al completed a retrospective study investigating selenium intakes through dietary questionnaires in 504 pregnant women (210 with hyperglycemia and 294 healthy controls) as well as measuring serum concentrations in a second cohort (71 hyperglycemic and 123 control women). A lower dietary
intake of selenium was observed in the hyperglycemic group, and in the second cohort, the selenium concentrations were significantly lower in the women who had impaired glucose tolerance; both dietary intakes and selenium concentration were negatively associated with gestational hyperglycemia in a multiple regression model (odds ratio, 0.97 and 0.92, respectively).\textsuperscript{150}

An inverse relationship between selenium concentrations and blood glucose concentrations has also been observed with out changes in insulin, suggesting that selenium may affect glucose metabolism downstream from insulin or possibly through independent energy-regulating pathways such as thyroid hormones.\textsuperscript{147} This relationship is unique to pregnancy because diabetes in nonpregnant subjects is associated with higher blood selenium concentrations.\textsuperscript{151,152} This association has also been reported specifically in type 2 diabetic subjects.\textsuperscript{153,154}

Conclusions

There are wide differences in selenium intake across diverse populations, depending on the selenium content of the soil and hence the selenium content in staple foodstuffs as well as on variations in individuals’ diets. Evidently the balance between intake, tissue concentration, and selenoenzyme synthesis is a very delicate one. This review illustrates the potential influence that selenium status has on many disorders relating to both animal and human reproduction and pregnancy. An important point to consider as limitations of many of the studies is the lack of correction for potential confounding factors. Such factors include other nutritional deficiencies, general health of the participants, family histories, etc. Obtaining detailed and accurate dietary and medical information is essential in any future studies. Many of the unsuccessful antioxidant trials for preeclampsia have focussed on the nonenzymatic antioxidants such as vitamins C and E,\textsuperscript{155-159} whereas current data potentially support the use of enzymatic antioxidants such as selenium as a viable option. However, before such trials can be conducted, further work is required on optimizing the timings, dosage, and type of selenium supplementation with or without other antioxidants to ensure the best possible chances of positive outcomes. Only when such issues have been examined and confirmed can a powered, carefully conducted, blinded, placebo-controlled RCT of selenium supplementation both in relation to infertility and pregnancy be completed in multiple centers in areas of known selenium deficiency. In conclusion, although persuasive evidence already exists to suggest that additional selenium would be beneficial in some of these disorders in selenium-insufficient women, results from intervention trials underway or planned have the potential to reinforce or refute the argument for increasing selenium intake.

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