Selenium in reproductive health

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This is a topical review summarising the increasing evidence for an association between inadequate dietary antioxidant selenium intake and several disorders of reproduction.

Short Title: Selenium in reproductive Health

Abstract

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Selenium is an essential trace element of importance to human biology and health. Increasing evidence suggests that this mineral plays an important role in normal growth and reproduction in animals and humans, and selenium supplementation is now recommended as part of public health policy in geographical areas with severe selenium deficiency in soil. Here, the biological functions of selenium are addressed prior to a detailed review of associations between selenium status and reproductive health. In many countries, selenium dietary intake falls below the recommended nutrient intakes (RNIs) and is inadequate to support maximal expression of the selenoenzymes. Numerous reports implicate selenium deficiency in several reproductive and obstetric complications including male and female infertility, miscarriage, pre-eclampsia, fetal growth restriction, preterm labour, gestational diabetes and obstetric cholestasis. Currently, there is inadequate information from the available small intervention studies to inform public health strategies. Larger intervention trials are required to reinforce or refute a beneficial role of selenium supplementation in disorders of reproductive health.

Keywords: Antioxidant, pregnancy, reproduction, selenium

Introduction

Selenium was first discovered in 1817 by Jöns Jacob Berzelius when investigating the chemicals responsible for outbreaks of ill health amongst workers in a Swedish sulphuric acid plant, which had switched from expensive, imported sulphur to a local product (Oldfield, 1987). The local product contained a contaminant which he named Selēnē, after the Greek goddess of the moon (McKenzie et al., 1998). Selenium lies directly below sulphur in the periodic table and above tellurium, and has similar chemical properties, as it binds with equal affinity to metals and non-metals, both directly and hydrochemically (Bauer, 1997, Burk and Levander, 2006). In 1957, Klaus Schwarz proved that selenium is an essential nutrient necessary for both normal growth and reproduction in animals through experiments demonstrating that minute amounts of selenium were protective against a form of liver necrosis in laboratory rats fed diets containing torula yeast as a protein source (Schwarz and Foltz, 1957). Dietary supplementation, by means of selenium-enriched fertilizer in crop production, foliar spraying of staple crops such as rice or soya beans or, directly, through multi-vitamin supplementation is now an accepted practice in areas of selenium deficiency, worldwide (Oldfield, 2002, Yang et al., 1988).

Selenium, amino acids and selenoproteins

The amino acids methionine and cysteine contain sulphur in the form of thiol groups. Selenium can replace the sulphur to form selenomethionine ([Se]Met) or selenocysteine ([Se]Cys or Sec) as a normal physiological process. A selenoprotein is any protein that includes a Sec or [Se]Met residue, which confers specific biological function. 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 which remain unclear (Reilly, 2006). The majority of selenium in the human diet is derived from [Se]Met in plant materials and both [Se]Met and Sec in animal products (Combs, 2001, Sunde, 1990). [Se]Met cannot be synthesised by higher animals, including humans, but after ingestion is non-specifically incorporated into proteins (e.g. haemoglobin, albumin) in place of methionine (Thomson et al., 1993). Selenophosphate is synthesised from selenide and ATP through the action of selenophosphate synthetase 2 (*SEPHS2*) and is the source of selenium from which Sec is then formed and co-translationally incorporated into selenoproteins at in-frame UGA codons. Sec has a lower pK_a than Cys and is more nucleophilic, so is more reactive. During protein catabolism, Sec is rapidly broken down to elemental selenium, leaving no free pool of cellular Sec. This has a biological advantage, since Sec can react with oxygen, thioredoxin and thioredoxin reductase, giving rise to rapid NADPH oxidation and the formation of damaging reactive oxygen species (ROS) (Lu and Holmgren, 2009).

The form in which selenium is present in food affects bioavailability and expression of the different selenoproteins. Organic selenium sources such as Se[Met] are more efficient at increasing the blood selenium concentration than inorganic selenium, such as selenite and selenate, but they appear to be equally adept at raising whole-blood glutathione peroxidase (GPx) activity in the long-term (Thomson et al., 1993). Bioavailability from the different selenium sources is also tissue dependent. Dietary protein is more effective than other sources in increasing measurable selenium status. High selenium consumption

leads to higher selenium content of proteins in the form of [Se]Met and Sec (Kohrle et al., 2005).

Selenite (SeO_3^{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 selenium derivatives that are excreted in urine, in expired air via the lungs and in faeces (Fig. 1) (Sunde, 1990, Ip, 1998). In humans these products of selenium metabolism are predominantly excreted in urine (Yang et al., 1989, Oster and Prellwitz, 1990). The proportion of selenium intake excreted in this manner depends on dietary intakes; when this is high, urinary excretion will also be high and vice versa (Robinson et al., 1973, Thomson and Robinson, 1986, Oster and Prellwitz, 1990).

There appears to be no homeostatic control of selenium absorption, which is unusual, in contrast, for example, to the complex regulation of iodine absorption (Kohrle et al., 2005, Reilly, 2006, Fairweather-Tait et al., 2010). 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 (Levander, 1987, Reilly, 2006). 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 (Drasch et al., 2000, Kohrle et al., 2005).

Selenoproteins, coded by twenty five selenoprotein genes in humans (Table 1) (Kryukov et al., 2003), exert multiple actions on endocrine, immune and inflammatory functions

(Beckett and Arthur, 2005, Thomson, 2004), in part because they have powerful antioxidant functions. The selenoenzymes have a Sec group at their active sites, which enables the formation of disulphide bonds (Burk and Levander, 2006); these function as a redox centre, participating in transfer of electrons between molecules (Flohe et al., 2000). Of the identified selenoproteins, three are iodothyronine deiodinases, which catalyse the removal of iodine from the 5 or 5' positions of iodothyronine substrates. This regulates the activation and inactivation of thyroid hormones in all tissues (Beckett and Arthur, 2005). A further three are the thioredoxin reductase family (TrxR1, TrxR2 and TrxR3). Their substrates, thioredoxin and thioredoxin peroxidase do not contain selenium. These constitute a powerful dithiol-disulphide system that regulates the cellular redox state (Hill et al., 2003, Burk et al., 2003, Mostert et al., 2003) (Table 1). The Trx system also regulates other antioxidants (such as heme oxygenase-1, methionine sulphoxide reductases, ascorbate (Vit C), tocopherol (Vit E), ubiquinone (Q10)), modulates several transcription factors (eg those involved in the maturation of p53) and regulates apoptosis and protein phosphorylation (Surai, 2006, Arner, 2009, Mostert et al., 2003).

Of particular importance to reproduction and pregnancy are the 6 antioxidant GPxs which play a pivotal role in reducing hydrogen peroxide (H_2O_2) and lipid peroxides to harmless products (water and alcohols; Fig. 2), thereby dampening the propagation of damaging ROS (Rotruck et al., 1973, Brigelius-Flohe et al., 2003). This important pathway of cellular protection has been demonstrated in all mammalian tissue examined (Allan et al., 1999, Knapen et al., 1999). As antioxidants, the GPxs help maintain membrane integrity, protect prostacylin production, and limit the propagation of oxidative damage to lipids,

lipoproteins, and DNA (Brigelius-Flohe et al., 2003). This pathway may also offer protection against development of several chronic diseases in which oxidative damage has been implicated, including atherosclerosis and certain cancers (Rayman, 2002, Combs, 2001, Brigelius-Flohe, 2008). However, the claims that selenium supplements contribute to the prevention of chronic disease currently lack substantial evidence based proof of efficacy. Indeed some of the larger trials have been negative, for example the recent randomised, placebo-controlled cancer chemoprevention trial (selenium and vitamin E cancer prevention trial; SELECT) demonstrated no benefit of supplements of selenium (200 μ/day) and vitamin E (400 IU/day) in prevention of prostate cancer in a total of 35,533 men (Lippman et al., 2009).

Dietary selenium

Plant foods are the major dietary sources of selenium in most countries (Rayman, 2000, Combs, 2001). Surveys suggest that wheat is the most efficient selenium accumulator of the common cereals, and is one of the most important selenium sources for man (Lyons et al., 2003, Reilly, 2006). The content in food depends on the selenium content of the soil where 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 US (Longnecker et al., 1991). Whether this degree of high intake has any positive health benefit is not known, but toxic effects supervene when intake exceeds ~ 850 μg/day (Goldhaber, 2003).

Other foods make a substantial contribution to selenium intake in northern Europe, particularly meat, poultry, and fish (a total of about 36% in the UK) (Ministry Of Agriculture Fisheries and Food, 1997). Thus it has been predicted that vegetarians or vegans are at specific risk of selenium deficiency (Reilly, 2006, Judd et al., 1997), but this claim is not fully substantiated.

Selenium incorporation into plants (initially), and then into animal tissues, not only depends on soil selenium content or geochemistry but also on soil pH, rainfall, land contour, the use of high-sulphur fertilisers and microbial activity; some bacteria can convert insoluble forms of selenium to soluble forms, which can then be taken up by plants (Diplock, 1993, Lyons et al., 2003). Selenium tends to be more concentrated in the soils of the drier regions of the world, where soil tends to be more alkaline; in acidic poorly aerated soils, selenium is relatively unavailable to plants as it is present mainly as insoluble selenite complexes (Lyons et al., 2003, Reilly, 2006).

In addition, in wetter regions, rain leaches selenium from the soil (Reilly, 2006). Selenium forms both inorganic and organic compounds and can be an oxidant as well as a reductant, an important factor in soil formation (Van Dorst and Peterson, 1984). Selenium's chemical adaptability accounts for its widespread occurrence in soils, plants, animals and humans (Bauer, 1997). Soil selenium concentrations range from 0.1 to more than 100 mg/Kg. However, most soils contain between 1.0 to 1.5 mg/Kg (0.1-0.6 mg/Kg is considered deficient) (Lyons et al., 2003, Combs, 2001).

Selenium deficiency

The optimal range of selenium intake to ensure biological benefit appears to be narrow and has still not been determined with certainty; however selenium deficiency has been studied in animals and humans (Van Vleet, 1980, Zachara et al., 1993a, Hurst et al., 2010). Selenium deficiency as assessed by dietary intake and/or blood selenium concentrations has been identified in people inhabiting geographical regions notable for low soil selenium content, such as volcanic regions and in Finland and New Zealand, where the reported average selenium intake is approximately 30-40 µg/day (Levander and Burk, 1994, Thomson, 2004). Animal selenium deficiency diseases have been routinely identified since the 1950s in livestock in countries that have low selenium soil conditions (Oldfield, 1997, Koller and Exon, 1986).

Human selenium deficiency diseases have been recognised in China and Tibet (Moreno-Reyes et al., 2003, Levander and Beck, 1997). Keshan disease, a reversible endemic cardiomyopathy, is characterised by focal myocardial necrosis often associated with inflammatory infiltrates and calcification. The disorder is exclusively endemic in selenium-deficient rural areas of China e.g. Keshan (Beck et al., 2003) and supplementation with selenium tablets (as sodium selenite) in pregnancy (Moore et al., 2000) provides highly effective protection against its development in susceptible women (Beck et al., 2003).

In Northern Karelia (Finland) very low blood selenium concentrations have also been reported in men with a high risk of myocardial infarction (MTT Agrifood Research

Finland, 2005). Smoking further compromises selenium status by decreasing the serum concentration of selenium, and erythrocyte GPx activity (Northrop-Clewes and Thurnham, 2007, Duthie et al., 1993). Low selenium status may exacerbate disease progression in conditions not otherwise associated with selenium-deficiency e.g. human immunodeficiency virus (HIV) infection and hepatitis C virus, although the mechanism which affords protection by selenium is not known (Rayman, 2000).

Dietary selenium intake in most parts of Europe is considerably lower than in the USA, mainly due to the European soils providing a poorer source of selenium (Thomson, 2004, Rayman, 2008). The reduction in consumption of wheat imported from the US in the European Union from the 1980s, as a result of the European Common Agricultural Policy, has been associated with a fall in daily selenium intake in the UK and other Western European countries over the last 20 years (Jackson et al., 2004).

Assessments of requirements, adequacy and intakes of selenium have been reviewed previously in detail (Rayman, 2008, Thomson, 2004). The recommended daily allowances (RDA) for both men and women in USA is 55 µg/day, rising to 60 µg/day for pregnant women (Institute of Medicine, 2000). The UK is still using the 1991 reference nutrient intakes (RNI) of 75 µg/day for adult men, 60 µg/day for adult women and 75 µg/day for lactating women (Department of Health, 1991). The Department of Health reviewed whether selenium intake should be higher in 1998 and then again in 2009, but concluded that the original figures were still applicable (Department of Health, 1998, Department of Health, 2009). The World Health Organisation (WHO) set its normative

requirement estimate (NR) at a lower value of 40 µg/day for men and 30 µg/day for women (WHO/FAO/IAEA, 1996). The RDA/RNI values have been determined from the intake believed necessary to maximise the activity of the antioxidant GPx in plasma, whereas the NR is based on selenium intake needed to achieve two-thirds of maximum activity of erythrocyte GPx (Thomson, 2004).

Selenium intake appears on average to be at or above the RDA in the US or Canada. A study in Maryland in 1981 reported that adults consumed an average of 81 µg/day of selenium (Welsh et al., 1981) and recently this has been estimated to be 108 µg/day for all US adults and 89 µg/day for women (Chun et al., 2010). A Canadian survey in 1975 reported intakes of 113 to 220 µg/day (Thompson et al., 1975); this was followed in 1998 by a report indicating consumption of between 98-224 µg/day (Gissel-Nielsen, 1998). Conversely, the UK selenium dietary intake is generally below the RNI; a dietary survey published by the UK Government over the period 1994 to 1995 indicated that the average intake was as low as 30–40 µg per day (Ministry Of Agriculture Fisheries and Food, 1997) a figure which had not improved in a survey conducted between 2008 and 2009 (Department of Health, 2009). Although it has been argued that UK intakes are sufficiently low to warrant government intervention (Rayman, 2000), a UK government expert committee concluded in 1998 that intervention was, at that time, not warranted (Department of Health, 1998). Whether, this conclusion pertains to the dietary intake in 2010 is uncertain and is worthy of investigation.

Selenium toxicity

Whilst selenium deficiency is prevalent and therefore the more predominant health issue, 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 (Twomey et al., 1977). Chronic toxicity of selenium in humans results in selenosis, a condition characterised by brittleness or loss of hair and nail loss, gastrointestinal problems, rashes, garlic breath odour, and nervous system abnormalities (Yang et al., 1983). In China, it has been reported that selenosis occurs with increased frequency in people who consumed selenium at levels above 850 μg/ day (Yang and Zhou, 1994). The Institute of Medicine, USA, has set a tolerable upper intake level for selenium at 400 μg/day for adults to prevent the risk of developing selenosis (Institute of Medicine, 2000). The European Commission and WHO have proposed the lower daily upper limit of 300 μg/day for adults (European Commission Health and Consumer Protection Directorate, 2000, WHO/FAO/IAEA, 1996).

Selenium in Reproductive Health

The role that selenium plays in both male and female reproduction is well recognised in animal husbandry (Reilly, 2006). Selenium is essential for male fertility, being required for testosterone biosynthesis and the formation and normal development of spermatozoa (Behne et al., 1996, Flohe, 2007). Studies using selenoprotein P-knockout mice support a requirement for selenium in testicular function (Hill et al., 2003) and animals fed selenium-deficient diets show impaired spermatozoan motility with flagellar defects localised primarily to the midpiece, decreasing the chance of fertilisation (Behne et al., 1996, Wu et al., 1973).

Testicular tissue contains high concentrations of selenium, predominantly as GPx4 and this provides the pivotal link between selenium, sperm quality and male fertility since GPx4 is a fundamental determinant of the architecture of the spermatozoan midpiece (Beckett and Arthur, 2005, Knapen et al., 1999), and is considered to shield developing sperm cells from oxidative DNA damage (Ursini et al., 1999, Safarinejad and Safarinejad, 2009). ROS have been implicated in male infertility because, through attack of the spermatozoa membrane, sperm viability is decreased.

Some evidence suggests that increasing selenium dietary intake increases antioxidant GPx activity, thereby increasing male fertility (Irvine, 1996). Bleau *et al's* study in 1984 was one of the first indications, in humans, that selenium deficiency may be related to male fertility, reporting an optimal range between 50 - 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 (Bleau et al., 1984). In Scotland (where mean selenium intakes are below requirements, ~30-40 μg per day) a placebo-controlled randomised control trial (RCT) of 64 men demonstrated that sperm quality and fertility improved after selenium supplementation (Scott et al., 1998). A placebo-controlled RCT from Tunisia of 54 infertile and 54 men on placebo also demonstrated the beneficial effects of a combination of vitamin E (400 mg) and selenium (225 μg) daily supplements for 3 months on improving sperm motility (Keskes-Ammar et al., 2003). In another recent placebo–controlled RCT in Iran of 468 infertile men, supplementation with 200 μg selenium orally daily for 26 weeks improved semen quality including sperm count,

298 concentration, morphology and motility, as well as plasma and semen selenium
299 concentrations (Safarinejad and Safarinejad, 2009). A recent review of the effect of oral
300 antioxidants (including selenium) on male subfertility concluded that supplementation
301 could improve sperm quality and/or pregnancy rates but recommended that large
302 adequately powered trials using individual antioxidants are required (Ross et al., 2010).
303
304 Data regarding selenium and female fertility are sparse. Paszkowski *et al*, completed a
305 study of 135 follicular fluid samples collected from 115 patients during transvaginal
306 oocyte retrieval; patients with unexplained infertility had significantly decreased
307 follicular selenium concentrations compared to those with tubal infertility or a known
308 male related cause of infertility (Paszkowski et al., 1995). A recent case-controlled study
309 from Turkey also found lower serum and follicular fluid selenium concentrations in 30
310 women undergoing IVF treatment compared to 13 age-matched non-pregnant control
311 women (Ozkaya et al., 2010). Another rather indirect indication of a role for selenium in
312 fertility comes from a small study of women with a history of unexplained infertility. In 6
313 of the 12 women investigated the red-cell magnesium content failed to normalises after 4
314 months of magnesium supplementation and was associated with a lower red-cell GPx
315 activity than that observed in the remaining 6 women whose red-cell magnesium regained
316 normality (Howard et al., 1994). Subsequent supplementation with magnesium and
317 selenium for 2 months achieved red-cell magnesium normalisation and increased red-cell
318 GPx activity and the women later (within 8 months) conceived with a healthy pregnancy
319 outcome (Howard et al., 1994). The authors theorised that failure to maintain cellular

magnesium homeostasis result from ROS induced cell permeability secondary to poor selenium status (Howard et al., 1994).

A combination of insulin, transferrin and selenium (ITS) is widely used as an adjuvant mixture in culture media for studies of ovarian and early pregnancy tissue, including human pre-antral follicles (Roy and Treacy, 1993, Abedelahi et al., 2010) or human fetal ovaries (Roig et al., 2006). The addition of selenium is reported to increase total antioxidant capacity and GPx activity, and decrease the levels of ROS, thus improving the *in vitro* development of follicles (Abedelahi et al., 2010).

In reinforcing the antioxidant properties of selenium, these studies highlight a potential role in female reproductive function. As concluded in a recent review, the relationship between oxidative stress, decreased female fertility, and selenium deficiency is an association which warrants further research activity (Ruder et al., 2009).

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 (Bradley and Hamilton-Fairley, 1998). 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 (Hirschfeld et al., 2007).

Miscarriages have been associated with selenium deficiency in veterinary practice (Stuart and Oehme, 1982), and selenium supplements prevent early pregnancy loss in sheep (Hidiroglou, 1979). In humans, a UK observational study reported significantly lower serum selenium concentrations in 40 women with 1st trimester miscarriage compared to 40 age-matched non-pregnant and 40 healthy gestation-matched women (Barrington et al., 1996). A similar finding was reported in another observational study from Turkey of 20 women with 1st trimester miscarriage compared to controls (Kocak et al., 1999). Red-cell and hair selenium concentrations are also reported to be lower in women with recurrent miscarriage (Al-Kunani et al., 2001, Kumar et al., 2002). Early pregnancy loss has been linked to reduced antioxidant protection of biological membranes and DNA and also to low concentrations of the selenium-dependent GPx (Barrington et al., 1997, Zachara et al., 2001, Jauniaux et al., 2006), and although speculative, women with recurrent pregnancy loss could potentially benefit from optimisation of selenium status.

Normal Pregnancy

During normal pregnancy, the selenium requirement is increased as a result of demands from the growing fetus (Smith and Picciano, 1986) and both inorganic and organic forms of selenium cross the placenta in humans and experimental animals (Shennan, 1987, Shennan, 1988, Nandakumaran et al., 2003, Nandakumaran et al., 2002). The RDA of selenium in pregnancy in the USA, calculated based on a fetal deposition of 4 μg/ day throughout pregnancy, is 60 μg/ day (Institute of Medicine, 2000).

In countries such as Poland and Yugoslavia where soil selenium content and dietary intake are low, maternal selenium concentrations and GPx activity fall during pregnancy, being the lowest at delivery compared with non-pregnant controls (Mihailovic et al., 2000, Zachara et al., 1993b). In contrast, in areas of very high soil selenium content e.g. South Dakota, it would appear that there is no gestational trend in serum selenium concentrations (Kundu et al., 1985). Babies generally have lower selenium concentrations compared to the mother (Gathwala et al., 2000, Mistry et al., 2008), which might be anticipated as selenium is transported via the placenta across a concentration gradient via an anion exchange pathway, (Shennan, 1987, Shennan, 1988).

Pre-eclampsia

Pre-eclampsia (*de novo* proteinuric hypertension) is estimated to occur in ~3% of all pregnancies and is a leading cause of maternal and perinatal mortality and morbidity in the Western world (Sibai et al., 2005, Steegers et al., 2010); together with other hypertensive disorders of pregnancy, pre-eclampsia is responsible for approximately 60,000 maternal deaths each year (Broughton Pipkin, 2001) and increases perinatal mortality five-fold (Roberts and Lain, 2002). Optimal outcome for the mother and child often dictates that the infant is delivered early leading to increased preterm delivery and low infant birthweight rates. Placental and maternal systemic oxidative stress are components of the syndrome (Poston, 2004) and contribute to a generalised maternal systemic inflammatory activation (Redman and Sargent, 2003). Placental ischaemia-

388 reperfusion injury has been implicated in excessive production of ROS, causing release of
389 placental factors that mediate the inflammatory responses (Hung and Burton, 2006).
390
391 Endothelial cell dysfunction has been implicated in the many clinical manifestations of
392 pre-eclampsia including hypertension and altered haemodynamics (Hubel, 1999, Poston,
393 2006). There is increased interest in the association between selenium status and pre-
394 eclampsia. In light of the association between oxidative stress and the prevalence of low
395 dietary selenium status worldwide, several studies have suggested that selenium
396 deficiency may be linked to pre-eclampsia.
397
398 The recent appreciation that nutrient-gene interactions may play a major role in
399 manifestation of hereditary disease traits (Hesketh, 2008) could be of relevance to the
400 association between selenium status and pre-eclampsia. Several genes which encode
401 selenoproteins demonstrate functional polymorphisms. Examples include GPx3,
402 functional polymorphisms of which decrease transcriptional activation, gene expression
403 and plasma protein activities (Voetsch et al., 2007a, Voetsch et al., 2007b). A single
404 nucleotide polymorphism within the 3'UTR of the *GPx4* gene (*GPx4c718t*) affects GPx
405 protein concentration and activity but also has differential effects on GPx3 and GPx1
406 when selenium supplementation is stopped (Meplan et al., 2008).
407
408 Selenoprotein S (also known as SEPS1 or VIMP), which contains a Sec residue at its
409 active site, is an anti-inflammatory protein that acts primarily to limit the damaging
410 consequences of endoplasmic reticulum stress (Ye et al., 2004), which has recently been

411 suggested to contribute to the development of pre-eclampsia (Burton et al., 2009). A
412 polymorphic variant in the SEPS1 locus has been associated with increased
413 cardiovascular disease morbidity in Finnish females (Alanne et al., 2007) and a 105G>A
414 promoter polymorphism associated with reduced function has been defined and is
415 significantly but not strongly associated with pre-eclampsia (Moses et al., 2008). Given
416 that pre-eclampsia has a familial component (Cincotta and Brennecke, 1998, Lie et al.,
417 1998, Chappell and Morgan, 2006), a high prevalence of these polymorphisms could, in
418 association with selenium deficiency be a major determinant of impaired antioxidant
419 defence in this disorder, through altered selenoprotein activity, and thereby contribute to
420 development of the disease through 'nutrigenomic' pathways. Genome wide association
421 studies of adequate size, such as that currently underway (Wellcome Trust case-control
422 consortium (WTCCC3) – pre-eclampsia;
423 http://www.wtccc.org.uk/ccc3/projects/ccc3_eclampsia.shtml) will be valuable in
424 determination of the prevalence of these and similar functional polymorphisms in women
425 affected by pre-eclampsia.
426
427 In the UK, where selenium dietary intake is low, our group and others have reported
428 selenium concentrations in pre-eclamptic pregnancies to be reduced in sera from the
429 mother (Atamer et al., 2005, Mistry et al., 2008) and fetus (Mistry et al., 2008) as well as
430 in amniotic fluid (Dawson et al., 1999) and in toenails (reflecting longer term selenium
431 stores) (Rayman et al., 2003), when compared to normal pregnant controls. A recent
432 retrospective study from Iran reported lower plasma selenium concentrations in 40 pre-
433 eclamptic compared to 40 control women (Maleki et al., 2011). Conversely, others have

434 shown no differences (Rayman et al., 1996) and in one study from the USA, higher sera
435 selenium concentrations have been reported in women with pre-eclampsia (Mahomed et
436 al., 2000). However, a reported lack of sensitivity of the assays used (Rayman et al.,
437 1996), or dependence of the maternal leucocyte selenium content in estimation of
438 selenium status (Mahomed et al., 2000) may confound interpretation of these studies.
439
440 Selenoprotein GPx activities in both maternal and cord plasma have also been shown to
441 be lower in pre-eclamptic pregnancies. A retrospective study of plasma taken from 25
442 pre-eclamptic and 15 healthy pregnant Turkish women in their 3rd trimester observed
443 significantly lower GPx levels in pre-eclampsia compared to controls (Yildirim et al.,
444 2004). A similar study, also from Turkey, retrospectively collected maternal blood just
445 before delivery, from 30 mild pre-eclamptic (defined as blood pressure $\geq$ 140/90 mm Hg
446 plus $\geq$ 300 mg/24 hours proteinuria); 30 severe pre-eclamptic (defined as $\geq$ 160/110 mm
447 Hg plus 5 g proteinuria in 24 hours) and 30 normal pregnant women. This study reported
448 lower concentrations of GPx in both pre-eclampsia groups compared to the controls
449 (Bulgan Kilicdag et al., 2005).
450
451 Several other retrospective studies from the USA (Wang and Walsh, 1996, Walsh and
452 Wang, 1993), Turkey (Atamer et al., 2005) and Australia (Vanderlelie et al., 2005) of
453 placental tissue collected from normal pregnancy and pre-eclampsia report a reduction in
454 GPx activity in pre-eclampsia. Our group recently conducted a retrospective cross-
455 sectional study in the UK of 25 pre-eclamptic women and 27 healthy controls, in which
456 maternal blood samples were collected before delivery, as well as cord blood and

placental tissue immediately after delivery (Mistry et al., 2008). Plasma concentrations of thiobarbituric acid reactive substances (TBARS; a marker for lipid peroxidation) were increased in maternal and cord plasma in the pre-eclamptic group. Moreover, total GPx activity in plasma and in placental tissue were significantly reduced in pre-eclampsia (Mistry et al., 2008). Further prospective, longitudinal studies are required to elucidate a 'cause or effect' relationship. If selenium deficiency is confirmed in women suffering from pre-eclampsia, and this continues to be linked with GPx inadequacy, selenium supplementation in pregnancy may be of benefit in prevention or amelioration of pre-eclampsia, a hypothesis which is currently being addressed in a RCT (see below).

Some small studies have attempted to assess the influence of selenium supplementation on the incidence of pregnancy related hypertensive disorders, Han *et al.,* conducted a small placebo-controlled RCT in Beijing, China, a population with a high risk of pregnancy-induced hypertension (PIH) and between 26%-27% and selenium deficiency. 52 women with known risk factors for PIH were randomised to selenium (100 μg/day) for 6-8 weeks during late pregnancy, and 48 were randomised to placebo (Han and Zhou, 1994). The selenium supplemented group had a reduced incidence of development of PIH (7.7%; 4/52) compared to the placebo group (22.7%; 11/48), and significantly increased maternal and cord blood selenium concentrations. Another very small prospective double-blind, placebo-controlled RCT study in Indonesia, reported lower rates of pre-eclampsia and/or PIH in women who were at increased risk of developing these conditions, after supplementation (n = 29) with a range of antioxidants and cofactors including selenium (100 μg) (Rumiris et al., 2006). Neither study adequately addressed

the role of supplementation on the incidence of pre-eclampsia. 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 pre-eclampsia although this didn't quite reach statistical significance (Tara et al., 2010).

There is no current consensus on the optimal dietary selenium supplement for use in clinical supplementation, since bioavailability and effects on expression of the various selenoproteins depend on the form of selenium product used (Rayman, 2008). A small UK based RCT of selenium supplementation (selenium in pregnancy; SPRINT) conducted by the Universities of Surrey and Oxford is ongoing. Although not powered to demonstrate clinical benefit this study is designed to assess the impact of selenium supplements on pre-eclampsia related biomarkers. Unselected primiparae are recruited between 12 and 16 weeks' gestation. The active treatment is 60 μg a day of selenium-enriched yeast, which is intended to normalise blood selenium concentrations. Most selenium in selenium-enriched yeast is in the form of [Se]Met, and supplementation with this yeast has, in the majority of reported studies been shown to increase the activity of the selenoenzymes (Rayman, 2004). If successful, a larger multicentre RCT adequately powered to detect differences in rates of pre-eclampsia will be needed to assess potential clinical benefit.

Preterm labour

Preterm labour (labour < 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 (Steer, 2005) and is likely to be of complex origin. Amongst the few studies to have investigated selenium and preterm labour, Dobrzynski *et al* from Poland reported lower maternal selenium concentrations and reduced maternal and cord plasma GPx activities in 46 women who delivered preterm compared to 42 women delivering at term (Dobrzynski et al., 1998). The low selenium concentrations and GPx activities in the blood of the preterm infants were proposed to contribute to respiratory distress syndrome, retinopathy of prematurity, increased haemolysis or other prematurity related conditions (Dobrzynski et al., 1998). A study from Germany of formula-fed preterm infants (gestational age < 32 weeks, birthweight < 1500 g) observed significantly lower mean plasma selenium concentrations compared to healthy term infants who were also formula-fed (Sievers et al., 2001). Another recent report from Iran of 30 preterm (gestational age <34 weeks) and 30 term infants (gestation age >37 weeks) also revealed significantly lower serum selenium concentrations in the preterm infants compared to term controls (Iranpour et al., 2009). A study from the USA of 13 preterm and 15 term infants found no differences in maternal plasma selenium concentrations, but also reported that preterm infants had lower selenium concentrations compared to term infants (Mask and Lane, 1993). 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 (Dobrzynski et al., 1998). Evidently, population selenium intake may explain some variation between studies.

Preterm premature (pre-labour) rupture of membranes (PPROM) is a major initiating factor in preterm labour and affects 10-12% of all pregnancies. PPROM is defined as premature rupture of chorioamniotic membranes before the onset of labour and is associated worldwide with increased rates of neonatal and maternal morbidity and mortality (Parry and Strauss, 1998, ACOG, 2007). Increased generation of ROS as well as antioxidant deficiency may play a important role in the pathophysiology of PPROM, which has been associated with enhancement of collagen degradation and subsequent damage to fetal membrane integrity (Wall et al., 2002, Woods, 2001, Woods et al., 2001). A potential association with selenium has been highlighted through a recent small prospective double blind, placebo-controlled RCT in Iran randomised 166 primigravid pregnant women in the first trimester of pregnancy to receive 100 μg/day selenium or placebo until delivery (Tara et al., 2010). The supplemented group demonstrated a significant increase in the mean serum selenium concentration and a reduction in the incidence of PPROM (Tara et al., 2010).

Fetal growth restriction

Fetal growth restriction or delivery of a small for gestational age infant (SGA) is defined as an individualised birthweight ratio below the 10^{th} percentile, and is associated with increased perinatal mortality and morbidity (Cetin et al., 2004). Some studies of SGA deliveries report a reduced placental selenium concentrations (Klapec et al., 2008), whereas others report higher (Osada et al., 2002, Zadrozna et al., 2009) or unchanged concentrations (Llanos and Ronco, 2009). Strambi *et al.,* demonstrated that in 81 SGA (both term and preterm) retrospective cases from Italy, infant plasma selenium

549 concentrations were significantly lower compared to adequate-for-gestational age (AGA)
550 infants (Strambi et al., 2004). Again geographical differences may explain the difference
551 between the selenium status in the different studies.
552 A recent investigation by our group in a cohort of adolescent pregnant women from two
553 UK inner cities (Baker et al., 2009) found lower plasma selenium concentrations in
554 mothers who delivered SGA infants compared to mothers who delivered AGA infants
555 (Mistry et al., 2010). A recent series of papers from North Dakota State University
556 suggest some protective effect of high selenium intake in nutrient-restricted pregnant
557 ewes on fetal birthweight and placental development (Lekatz et al., 2010). We are not
558 aware of any ongoing studies investigating maternal and fetal selenium status in relation
559 to fetal growth restriction although these observations would warrant a larger prospective
560 study especially focussing on adolescent pregnant women and those residing in selenium-
561 deficient populations.
562
563 *Obstetric cholestasis*
564 Obstetric cholestasis (OC) is a serious complication of pregnancy and affects
565 approximately 4,500 women per year in the UK. Affected women develop itching,
566 otherwise-unexplained elevation of plasma liver enzymes and of serum bile acids and
567 occasionally jaundice. OC is associated with an increased risk of premature delivery and
568 fetal distress and is believed to be an important cause of stillbirth (Gurung et al., 2009).
569
570 Selenium was first linked with OC in 1987 when Kauppila *et al* demonstrated that serum
571 selenium concentrations were significantly lower in 12 Finnish women with OC when

compared to 12 normal pregnancies during the last trimester and postpartum (Kauppila et al., 1987). Furthermore they also showed GPx activities to be decreased, showing a significant positive correlation with selenium concentration (Kauppila et al., 1987). Thus, it has been hypothesised that inadequate antioxidant protection may lead to hepatocyte oxidative damage and reduce excretion of bile (Akerboom et al., 1984). These initial results have been confirmed and extended in a study of 21 women with OC 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 (Reyes et al., 2000).

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is one of the more common diseases in pregnancy, affecting between 2% and 5% of pregnant women and is associated with birthweights above the 90th centile, increased levels of primary Caesarean deliveries and neonatal hypoglycaemia (Gilmartin et al., 2008). GDM is defined as a deficient insulin supply relative to the increased demands that are characteristic of pregnancy (Metzger et al., 2007). 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. A significant proportion of GDM women develop type 2 diabetes 5-16 years after pregnancy (17-63% risk) (Kjos et al., 1995, O'Sullivan and Mahan, 1964, Mestman et al., 1972).

A link between selenium and glucose metabolism has been observed previously in animal studies (Becker et al., 1996, McNeill et al., 1991, Ezaki, 1990) and selenium administered to streptozotocin-diabetic rats showed a restoration of glycemic control and a

595 modification of the activity of a range of enzymes involved in hepatic glycolysis and
596 glyconeogenesis (Becker et al., 1996). Several studies from China, Kuwait, Turkey and
597 the USA have shown a decrease in maternal plasma selenium concentrations in women
598 with GDM (Tan et al., 2001, Hawkes et al., 2004, Kilinc et al., 2008, Al-Saleh et al.,
599 2004). Bo *et al* completed a retrospective study investigating selenium intakes through
600 dietary questionnaires in 504 pregnant women (210 with hyperglycemia and 294 healthy
601 controls) as well as measuring serum concentrations in a second cohort (71
602 hyperglycemic and 123 controls) (Bo et al., 2005). A lower dietary intake of selenium
603 was observed in the hyperglycaemic group and in the second cohort, selenium
604 concentrations were significantly lower in the women who had impaired glucose
605 tolerance; both dietary intakes and selenium concentration were negatively associated
606 with gestational hyperglycemia in a multiple regression model (odds ratio 0.97 and 0.92
607 respectively) (Bo et al., 2005).
608
609 An inverse relationship between selenium concentrations and blood glucose
610 concentrations has also been observed (Kilinc et al., 2008, Tan et al., 2001, Hawkes et al.,
611 2004), but was not accompanied by changes in insulin (Hawkes et al 2004) suggesting
612 that selenium may affect glucose metabolism downstream from insulin, or possibly
613 through independent energy regulating pathways such as thyroid hormones (Hawkes et
614 al., 2004). This relationship is unique to pregnancy: diabetes in non-pregnant subjects is
615 associated with higher blood selenium concentrations (Laclaustra et al., 2009).
616
617 **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. Both deficiency and excess are damaging to health. In turn, varying intakes are associated with differences in selenoprotein and selenoenzyme expression in different tissues. This must be taken into account when comparing data from different countries or populations. 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. While persuasive evidence already exists to suggest that additional selenium would be beneficial in some of these disorders, results from intervention trials underway or planned have the potential to reinforce or refute the argument for increasing selenium intake.

641 **References**

642 Abedelahi, A, Salehnia, M, Allameh, AA & Davoodi, D (2010) Sodium selenite improves
643 the in vitro follicular development by reducing the reactive oxygen species level
644 and increasing the total antioxidant capacity and glutathione peroxide activity.
645 *Hum Reprod*.
646 ACOG (2007) Premature rupture of membranes. ACOG Practice Bulletin. No. 80.
647 Akerboom, TP, Bilzer, M & Sies, H (1984) Relation between glutathione redox changes
648 and biliary excretion of taurocholate in perfused rat liver. *J Biol Chem* **259,** 5838-
649 5843.
650 Al-Kunani, AS, Knight, R, Haswell, SJ, Thompson, JW & Lindow, SW (2001) The
651 selenium status of women with a history of recurrent miscarriage. *BJOG* **108,**
652 1094-1097.
653 Al-Saleh, E, Nandakumaran, M, Al-Shammari, M & Al-Harouny, A (2004) Maternal-
654 fetal status of copper, iron, molybdenum, selenium and zinc in patients with
655 gestational diabetes. *J Matern Fetal Neonatal Med* **16,** 15-21.
656 Alanne, M, Kristiansson, K, Auro, K, Silander, K, Kuulasmaa, K, Peltonen, L, et al.
657 (2007) Variation in the selenoprotein S gene locus is associated with coronary
658 heart disease and ischemic stroke in two independent Finnish cohorts. *Hum Genet*
659 **122,** 355-365.
660 Allan, CB, Lacourciere, GM & Stadtman, TC (1999) Responsiveness of selenoproteins to
661 dietary selenium. *Annu Rev Nutr* **19,** 1-16.
662 Arner, ES (2009) Focus on mammalian thioredoxin reductases--important selenoproteins
663 with versatile functions. *Biochim Biophys Acta* **1790,** 495-526.
664 Atamer, Y, Kocyigit, Y, Yokus, B, Atamer, A & Erden, AC (2005) Lipid peroxidation,
665 antioxidant defense, status of trace metals and leptin levels in preeclampsia. *Eur J*
666 *Obstet Gynecol Reprod Biol* **119,** 60-66.
667 Baker, PN, Wheeler, SJ, Sanders, TA, Thomas, JE, Hutchinson, CJ, Clarke, K, et al.
668 (2009) A prospective study of micronutrient status in adolescent pregnancy. *Am J*
669 *Clin Nutr* **89,** 1114-1124.
670 Barrington, JW, Lindsay, P, James, D, Smith, S & Roberts, A (1996) Selenium deficiency
671 and miscarriage: a possible link? *Br J Obstet Gynaecol* **103,** 130-132.
672 Barrington, JW, Taylor, M, Smith, S & Bowen-Simpkins, P (1997) Selenium and
673 recurrent miscarriage. *J Obstet Gynaecol* **17,** 199-200.
674 Bauer, F (1997) Selenium and Soils in the Western United States. In: Electronic Green
675 Journal. eScholarship Repository; UCLA Library, University of California, Los
676 Angeles.
677 Beck, MA, Levander, OA & Handy, J (2003) Selenium deficiency and viral infection. *J*
678 *Nutr* **133,** 1463S-1467S.
679 Becker, DJ, Reul, B, Ozcelikay, AT, Buchet, JP, Henquin, JC & Brichard, SM (1996)
680 Oral selenate improves glucose homeostasis and partly reverses abnormal
681 expression of liver glycolytic and gluconeogenic enzymes in diabetic rats.
682 *Diabetologia* **39,** 3-11.
683 Beckett, GJ & Arthur, JR (2005) Selenium and endocrine systems. *J Endocrinol* **184,**
684 455-465.

685 Behne, D, Weiler, H & Kyriakopoulos, A (1996) Effects of selenium deficiency on
686 testicular morphology and function in rats. *J Reprod Fertil* **106,** 291-297.
687 Bleau, G, Lemarbre, J, Faucher, G, Roberts, KD & Chapdelaine, A (1984) Semen
688 selenium and human fertility. *Fertil Steril* **42,** 890-894.
689 Bo, S, Lezo, A, Menato, G, Gallo, ML, Bardelli, C, Signorile, A, et al. (2005) Gestational
690 hyperglycemia, zinc, selenium, and antioxidant vitamins. *Nutrition* **21,** 186-191.
691 Bradley, E & Hamilton-Fairley, D (1998) Managing miscarriage in early pregnancy
692 assessment units. *Hosp Med* **59,** 451-456.
693 Brigelius-Flohe, R (2008) Selenium compounds and selenoproteins in cancer. *Chem*
694 *Biodivers* **5,** 389-395.
695 Brigelius-Flohe, R, Banning, A & Schnurr, K (2003) Selenium-dependent enzymes in
696 endothelial cell function. *Antioxid Redox Signal* **5,** 205-215.
697 Broughton Pipkin, F (2001) Risk factors for preeclampsia. *N Engl J Med* **344,** 925-926.
698 Bulgan Kilicdag, E, Ay, G, Celik, A, Ustundag, B, Ozercan, I & Simsek, M (2005)
699 Oxidant-antioxidant system changes relative to placental-umbilical pathology in
700 patients with preeclampsia. *Hypertens Pregnancy* **24,** 147-157.
701 Burk, RF, Hill, KE & Motley, AK (2003) Selenoprotein metabolism and function:
702 evidence for more than one function for selenoprotein P. *J Nutr* **133,** 1517S-
703 1520S.
704 Burk, RF & Levander, OA (2006) Selenium. In: Modern nutrition in health and disease.
705 eds Shils, ME, Shike, M, Ross, AC, Caballero, B & Cousins, RJ) Tenth edn.
706 Lippincott Williams & Wilkins, Philadelphia.
707 Burton, GJ, Yung, HW, Cindrova-Davies, T & Charnock-Jones, DS (2009) Placental
708 endoplasmic reticulum stress and oxidative stress in the pathophysiology of
709 unexplained intrauterine growth restriction and early onset preeclampsia. *Placenta*
710 **30 Suppl A,** S43-48.
711 Cetin, I, Foidart, JM, Miozzo, M, Raun, T, Jansson, T, Tsatsaris, V, et al. (2004) Fetal
712 growth restriction: a workshop report. *Placenta* **25,** 753-757.
713 Chappell, S & Morgan, L (2006) Searching for genetic clues to the causes of pre-
714 eclampsia. *Clin Sci (Lond)* **110,** 443-458.
715 Chun, OK, Floegel, A, Chung, SJ, Chung, CE, Song, WO & Koo, SI (2010) Estimation
716 of antioxidant intakes from diet and supplements in U.S. adults. *J Nutr* **140,** 317-
717 324.
718 Cincotta, RB & Brennecke, SP (1998) Family history of pre-eclampsia as a predictor for
719 pre-eclampsia in primigravidas. *Int J Gynaecol Obstet* **60,** 23-27.
720 Combs, GF, Jr. (2001) Selenium in global food systems. *Br J Nutr* **85,** 517-547.
721 Dawson, EB, Evans, DR & Nosovitch, J (1999) Third-trimester amniotic fluid metal
722 levels associated with preeclampsia. *Arch Environ Health* **54,** 412-415.
723 Department of Health (1991) Dietary reference values for food energy and nutrients for
724 the United Kingdom. Report on Social Subjects no. 41. London.
725 Department of Health (1998) Statement from the Committe on Medical Aspects of Food
726 and Nutrition Policy on Selenium. The Stationery Office, London.
727 Department of Health (2009) National Diet and Nutrition Survey. eds Bates, B, Lennox,
728 A & Swan, G). Deapartment of Health & Food Standards Agency.
729 Diplock, AT (1993) Indexes of selenium status in human populations. *Am J Clin Nutr* **57,**
730 256S-258S.

731 Dobrzynski, W, Trafikowska, U, Trafikowska, A, Pilecki, A, Szymanski, W & Zachara,
732 BA (1998) Decreased selenium concentration in maternal and cord blood in
733 preterm compared with term delivery. *Analyst* **123,** 93-97.
734 Drasch, G, Mail der, S, Schlosser, C & Roider, G (2000) Content of non-mercury-
735 associated selenium in human tissues. *Biol Trace Elem Res* **77,** 219-230.
736 Duthie, GG, Arthur, JR, Beattie, JA, Brown, KM, Morrice, PC, Robertson, JD, et al.
737 (1993) Cigarette smoking, antioxidants, lipid peroxidation, and coronary heart
738 disease. *Ann N Y Acad Sci* **686,** 120-129.
739 European Commission Health and Consumer Protection Directorate (2000) Opinion of
740 the Scientific Committee on Food on the tolerable upper intake level of selenium.
741 SCF/CS/NUT/UPPLEV/25 Final
742 Ezaki, O (1990) The insulin-like effects of selenate in rat adipocytes. *J Biol Chem* **265,**
743 1124-1128.
744 Fairweather-Tait, SJ, Collings, R & Hurst, R (2010) Selenium bioavailability: current
745 knowledge and future research requirements. *Am J Clin Nutr*.
746 Flohe, L (2007) Selenium in mammalian spermiogenesis. *Biol Chem* **388,** 987-995.
747 Flohe, L, Andreesen, JR, Brigelius-Flohe, R, Maiorino, M & Ursini, F (2000) Selenium,
748 the element of the moon, in life on earth. *IUBMB Life* **49,** 411-420.
749 Gathwala, G, Yadav, OP, Singh, I & Sangwan, K (2000) Maternal and cord plasma
750 selenium levels in full-term neonates. *Indian J Pediatr* **67,** 729-731.
751 Gilmartin, AB, Ural, SH & Repke, JT (2008) Gestational diabetes mellitus. *Rev Obstet*
752 *Gynecol* **1,** 129-134.
753 Gissel-Nielsen, G (1998) Effects of selenium supplementation of food crops In:
754 Environmental Chemistry of Selenium. eds Frankenberger Jr, WT & Engberg,
755 RA). Marcel Dekker, New York.
756 Goldhaber, SB (2003) Trace element risk assessment: essentiality vs. toxicity. *Regul*
757 *Toxicol Pharmacol* **38,** 232-242.
758 Gurung, V, Williamson, C, Chappell, L, Chambers, J, Briley, A, Broughton Pipkin, F, et
759 al. (2009) Pilot study for a trial of ursodeoxycholic acid and/or early delivery for
760 obstetric cholestasis. *BMC Pregnancy Childbirth* **9,** 19.
761 Han, L & Zhou, SM (1994) Selenium supplement in the prevention of pregnancy induced
762 hypertension. *Chin Med J (Engl)* **107,** 870-871.
763 Hawkes, WC, Alkan, Z, Lang, K & King, JC (2004) Plasma selenium decrease during
764 pregnancy is associated with glucose intolerance. *Biol Trace Elem Res* **100,** 19-29.
765 Hesketh, J (2008) Nutrigenomics and selenium: gene expression patterns, physiological
766 targets, and genetics. *Annu Rev Nutr* **28,** 157-177.
767 Hidiroglou, M (1979) Trace element deficiencies and fertility in ruminants: a review. *J*
768 *Dairy Sci* **62,** 1195-1206.
769 Hill, KE, Zhou, J, McMahan, WJ, Motley, AK, Atkins, JF, Gesteland, RF, et al. (2003)
770 Deletion of selenoprotein P alters distribution of selenium in the mouse. *J Biol*
771 *Chem* **278,** 13640-13646.
772 Hirschfeld, AF, Jiang, R, Robinson, WP, McFadden, DE & Turvey, SE (2007) Toll-like
773 receptor 4 polymorphisms and idiopathic chromosomally normal miscarriage.
774 *Hum Reprod* **22,** 440-443.

775 Howard, JM, Davies, S & Hunnisett, A (1994) Red cell magnesium and glutathione
776 peroxidase in infertile women--effects of oral supplementation with magnesium
777 and selenium. *Magnes Res* **7,** 49-57.
778 Hubel, CA (1999) Oxidative stress in the pathogenesis of preeclampsia. *Proc Soc Exp*
779 *Biol Med* **222,** 222-235.
780 Hung, TH & Burton, GJ (2006) Hypoxia and reoxygenation: a possible mechanism for
781 placental oxidative stress in preeclampsia. *Taiwan J Obstet Gynecol* **45,** 189-200.
782 Hurst, R, Armah, CN, Dainty, JR, Hart, DJ, Teucher, B, Goldson, AJ, et al. (2010)
783 Establishing optimal selenium status: results of a randomized, double-blind,
784 placebo-controlled trial. *Am J Clin Nutr* **91,** 923-931.
785 Institute of Medicine (2000) Food and Nutrition Board. In: Dietary Reference Intakes for
786 Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press
787 Washington DC.
788 Ip, C (1998) Lessons from basic research in selenium and cancer prevention. *J Nutr* **128,**
789 1845-1854.
790 Iranpour, R, Zandian, A, Mohammadizadeh, M, Mohammadzadeh, A, Balali-Mood, M &
791 Hajiheydari, M (2009) Comparison of maternal and umbilical cord blood
792 selenium levels in term and preterm infants. *Zhongguo Dang Dai Er Ke Za Zhi*
793 **11,** 513-516.
794 Irvine, DS (1996) Glutathione as a treatment for male infertility. *Rev Reprod* **1,** 6-12.
795 Jackson, MJ, Dillon, SA, Broome, CS, McArdle, A, Hart, CA & McArdle, F (2004) Are
796 there functional consequences of a reduction in selenium intake in UK subjects?
797 *Proc Nutr Soc* **63,** 513-517.
798 Jauniaux, E, Poston, L & Burton, GJ (2006) Placental-related diseases of pregnancy:
799 Involvement of oxidative stress and implications in human evolution. *Hum*
800 *Reprod Update* **12,** 747-755.
801 Judd, PA, Long, A, Butcher, M, Caygill, CP & Diplock, AT (1997) Vegetarians and
802 vegans may be most at risk from low selenium intakes. *BMJ* **314,** 1834a-.
803 Kauppila, A, Korpela, H, Makila, UM & Yrjanheikki, E (1987) Low serum selenium
804 concentration and glutathione peroxidase activity in intrahepatic cholestasis of
805 pregnancy. *Br Med J (Clin Res Ed)* **294,** 150-152.
806 Keskes-Ammar, L, Feki-Chakroun, N, Rebai, T, Sahnoun, Z, Ghozzi, H, Hammami, S, et
807 al. (2003) Sperm oxidative stress and the effect of an oral vitamin E and selenium
808 supplement on semen quality in infertile men. *Arch Androl* **49,** 83-94.
809 Kilinc, M, Guven, MA, Ezer, M, Ertas, IE & Coskun, A (2008) Evaluation of serum
810 selenium levels in Turkish women with gestational diabetes mellitus, glucose
811 intolerants, and normal controls. *Biol Trace Elem Res* **123,** 35-40.
812 Kjos, SL, Peters, RK, Xiang, A, Henry, OA, Montoro, M & Buchanan, TA (1995)
813 Predicting future diabetes in Latino women with gestational diabetes. Utility of
814 early postpartum glucose tolerance testing. *Diabetes* **44,** 586-591.
815 Klapec, T, Cavar, S, Kasac, Z, Rucevic, S & Popinjac, A (2008) Selenium in placenta
816 predicts birth weight in normal but not intrauterine growth restriction pregnancy. *J*
817 *Trace Elem Med Biol* **22,** 54-58.
818 Knapen, MF, Zusterzeel, PL, Peters, WH & Steegers, EA (1999) Glutathione and
819 glutathione-related enzymes in reproduction. A review. *Eur J Obstet Gynecol*
820 *Reprod Biol* **82,** 171-184.

821 Kocak, I, Aksoy, E & Ustun, C (1999) Recurrent spontaneous abortion and selenium
822 deficiency. *Int J Gynaecol Obstet* **65,** 79-80.
823 Kohrle, J, Jakob, F, Contempre, B & Dumont, JE (2005) Selenium, the thyroid, and the
824 endocrine system. *Endocr Rev* **26,** 944-984.
825 Koller, LD & Exon, JH (1986) The two faces of selenium-deficiency and toxicity--are
826 similar in animals and man. *Can J Vet Res* **50,** 297-306.
827 Kryukov, GV, Castellano, S, Novoselov, SV, Lobanov, AV, Zehtab, O, Guigo, R, et al.
828 (2003) Characterization of mammalian selenoproteomes. *Science* **300,** 1439-1443.
829 Kumar, KS, Kumar, A, Prakash, S, Swamy, K, Jagadeesan, V & Jyothy, A (2002) Role of
830 red cell selenium in recurrent pregnancy loss. *J Obstet Gynaecol* **22,** 181-183.
831 Kundu, N, Parke, P, Palmer, IS, Olson, O & Petersen, LP (1985) Distribution of serum
832 selenium, copper, and zinc in normal human pregnancy. *Arch Environ Health* **40,**
833 268-273.
834 Laclaustra, M, Navas-Acien, A, Stranges, S, Ordovas, JM & Guallar, E (2009) Serum
835 selenium concentrations and diabetes in U.S. adults: National Health and
836 Nutrition Examination Survey (NHANES) 2003-2004. *Environ Health Perspect*
837 **117,** 1409-1413.
838 Lekatz, LA, Caton, JS, Taylor, JB, Reynolds, LP, Redmer, DA & Vonnahme, KA (2010)
839 Maternal selenium supplementation and timing of nutrient restriction in pregnant
840 sheep: effects on maternal endocrine status and placental characteristics. *J Anim*
841 *Sci* **88,** 955-971.
842 Levander, OA (1987) Selenium. In: Trace Elements in Human and Animal Nutrition. (ed
843 Orlando, FL). Academic Press Inc, London.
844 Levander, OA & Beck, MA (1997) Interacting nutritional and infectious etiologies of
845 Keshan disease. Insights from coxsackie virus B-induced myocarditis in mice
846 deficient in selenium or vitamin E. *Biol Trace Elem Res* **56,** 5-21.
847 Levander, OA & Burk, RF (1994) Selenium. In: Modern Nutrition in Health and Disease.
848 eds Shils, ME, Olson, JA & Shike, M) 8th edn. Lea and Febiger, Philadelphia.
849 Lie, RT, Rasmussen, S, Brunborg, H, Gjessing, HK, Lie-Nielsen, E & Irgens, LM (1998)
850 Fetal and maternal contributions to risk of pre-eclampsia: population based study.
851 *BMJ* **316,** 1343-1347.
852 Lippman, SM, Klein, EA, Goodman, PJ, Lucia, MS, Thompson, IM, Ford, LG, et al.
853 (2009) Effect of selenium and vitamin E on risk of prostate cancer and other
854 cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*
855 **301,** 39-51.
856 Llanos, MN & Ronco, AM (2009) Fetal growth restriction is related to placental levels of
857 cadmium, lead and arsenic but not with antioxidant activities. *Reprod Toxicol* **27,**
858 88-92.
859 Longnecker, MP, Taylor, PR, Levander, OA, Howe, M, Veillon, C, McAdam, PA, et al.
860 (1991) Selenium in diet, blood, and toenails in relation to human health in a
861 seleniferous area. *Am J Clin Nutr* **53,** 1288-1294.
862 Lu, J & Holmgren, A (2009) Selenoproteins. *J Biol Chem* **284,** 723-727.
863 Lyons, G, Stangoulis, J & Graham, R (2003) Nutriprevention of Disease with High-
864 Selenium Wheat. *Journal of Australasian College of Nutritional Medicine* **22,** 3-9.

865 Mahomed, K, Williams, MA, Woelk, GB, Mudzamiri, S, Madzime, S, King, IB, et al.
866 (2000) Leukocyte selenium, zinc, and copper concentrations in preeclamptic and
867 normotensive pregnant women. *Biol Trace Elem Res* **75,** 107-118.
868 Maleki, A, Fard, MK, Zadeh, DH, Mamegani, MA, Abasaizadeh, S & Mazloomzadeh, S
869 (2011) The Relationship between Plasma Level of Se and Preeclampsia.
870 *Hypertens Pregnancy*.
871 Mask, G & Lane, HW (1993) Selected measures of selenium status in full-term and
872 preterm neonates, their mothers and non-pregnant women. *Nutrition Research* **13,**
873 901-911.
874 McKenzie, RC, Rafferty, TS & Beckett, GJ (1998) Selenium: an essential element for
875 immune function. *Immunol Today* **19,** 342-345.
876 McNeill, JH, Delgatty, HL & Battell, ML (1991) Insulinlike effects of sodium selenate in
877 streptozocin-induced diabetic rats. *Diabetes* **40,** 1675-1678.
878 Meplan, C, Crosley, LK, Nicol, F, Horgan, GW, Mathers, JC, Arthur, JR, et al. (2008)
879 Functional effects of a common single-nucleotide polymorphism (GPX4c718t) in
880 the glutathione peroxidase 4 gene: interaction with sex. *Am J Clin Nutr* **87,** 1019-
881 1027.
882 Mestman, JH, Anderson, GV & Guadalupe, V (1972) Follow-up study of 360 subjects
883 with abnormal carbohydrate metabolism during pregnancy. *Obstet Gynecol* **39,**
884 421-425.
885 Metzger, BE, Buchanan, TA, Coustan, DR, de Leiva, A, Dunger, DB, Hadden, DR, et al.
886 (2007) Summary and recommendations of the Fifth International Workshop-
887 Conference on Gestational Diabetes Mellitus. *Diabetes Care* **30 Suppl 2,** S251-
888 260.
889 Mihailovic, M, Cvetkovic, M, Ljubic, A, Kosanovic, M, Nedeljkovic, S, Jovanovic, I, et
890 al. (2000) Selenium and malondialdehyde content and glutathione peroxidase
891 activity in maternal and umbilical cord blood and amniotic fluid. *Biol Trace Elem*
892 *Res* **73,** 47-54.
893 Ministry Of Agriculture Fisheries and Food (1997) Dietary Intake of Selenium. (ed Joint
894 Food Safety and Standards Group). H.M. Stationery Office, London.
895 Mistry, HD, Kurlak, LO, Young, SY, Briley, AL, Broughton Pipkin, F & Poston, L
896 (2010) Reduced plasma selenium in adolescent mothers with small for gestational
897 age infants; impact of smoking and ethnicity. In: Society for Gynecologic
898 Investigation. Reproductive Sciences, Orlando.
899 Mistry, HD, Wilson, V, Ramsay, MM, Symonds, ME & Broughton Pipkin, F (2008)
900 Reduced selenium concentrations and glutathione peroxidase activity in pre-
901 eclamptic pregnancies. *Hypertension* **52,** 881-888.
902 Moore, MA, Wander, RC, Xia, YM, Du, SH, Butler, JA & Whanger, PD (2000)
903 Selenium supplementation of Chinese women with habitually low selenium intake
904 increases plasma selenium, plasma glutathione peroxidase activity, and milk
905 selenium, but not milk glutathione peroxidase activity. *J Nutr Biochem* **11,** 341-
906 347.
907 Moreno-Reyes, R, Mathieu, F, Boelaert, M, Begaux, F, Suetens, C, Rivera, MT, et al.
908 (2003) Selenium and iodine supplementation of rural Tibetan children affected by
909 Kashin-Beck osteoarthropathy. *Am J Clin Nutr* **78,** 137-144.

910 Moses, EK, Johnson, MP, Tommerdal, L, Forsmo, S, Curran, JE, Abraham, LJ, et al.
911 (2008) Genetic association of preeclampsia to the inflammatory response gene
912 SEPS1. *Am J Obstet Gynecol* **198,** 336 e331-335.
913 Mostert, V, Hill, KE & Burk, RF (2003) Loss of activity of the selenoenzyme thioredoxin
914 reductase causes induction of hepatic heme oxygenase-1. *FEBS Lett* **541,** 85-88.
915 MTT Agrifood Research Finland (2005) Fertilization has guaranteed the selenium intake
916 of Finns.
917 Nandakumaran, M, Dashti, HM, Al-Saleh, E & Al-Zaid, NS (2003) Transport kinetics of
918 zinc, copper, selenium, and iron in perfused human placental lobule in vitro. *Mol*
919 *Cell Biochem* **252,** 91-96.
920 Nandakumaran, M, Dashti, HM & Al-Zaid, NS (2002) Maternal-fetal transport kinetics
921 of copper, selenium, magnesium and iron in perfused human placental lobule: in
922 vitro study. *Mol Cell Biochem* **231,** 9-14.
923 Northrop-Clewes, CA & Thurnham, DI (2007) Monitoring micronutrients in cigarette
924 smokers. *Clin Chim Acta* **377,** 14-38.
925 O'Sullivan, JB & Mahan, CM (1964) Criteria for the Oral Glucose Tolerance Test in
926 Pregnancy. *Diabetes* **13,** 278-285.
927 Oldfield, JE (1987) The two faces of selenium. *J Nutr* **117,** 2002-2008.
928 Oldfield, JE (1997) Observations on the efficacy of various forms of selenium for
929 livestock: a review. *Biomed Environ Sci* **10,** 280-291.
930 Oldfield, JE (2002) A brief history of selenium research: from alkali disease to prostate
931 cancer (from poison to prevention). American Society of Animal Science.
932 Osada, H, Watanabe, Y, Nishimura, Y, Yukawa, M, Seki, K & Sekiya, S (2002) Profile
933 of trace element concentrations in the feto-placental unit in relation to fetal
934 growth. *Acta Obstet Gynecol Scand* **81,** 931-937.
935 Oster, O & Prellwitz, W (1990) The renal excretion of selenium. *Biol Trace Elem Res* **24,**
936 119-146.
937 Ozkaya, MO, Naziroglu, M, Barak, C & Berkkanoglu, M (2010) Effects of
938 Multivitamin/Mineral Supplementation on Trace Element Levels in Serum and
939 Follicular Fluid of Women Undergoing in Vitro Fertilization (IVF). *Biol Trace*
940 *Elem Res*.
941 Parry, S & Strauss, JF, 3rd (1998) Premature rupture of the fetal membranes. *N Engl J*
942 *Med* **338,** 663-670.
943 Paszkowski, T, Traub, AI, Robinson, SY & McMaster, D (1995) Selenium dependent
944 glutathione peroxidase activity in human follicular fluid. *Clin Chim Acta* **236,**
945 173-180.
946 Patrick, L (2004) Selenium biochemistry and cancer: a review of the literature. *Altern*
947 *Med Rev* **9,** 239-258.
948 Poston, L (2004) The Role of Oxidative Stress. In: Pre-eclampsia. eds Critchley, H,
949 MacLean, A, Poston, L & Walker, J). RCOG Press, London.
950 Poston, L (2006) Endothelial dysfunction in pre-eclampsia. *Pharmacol Rep* **58 Suppl,** 69-
951 74.
952 Rayman, MP (2000) The importance of selenium to human health. *Lancet* **356,** 233-241.
953 Rayman, MP (2002) The argument for increasing selenium intake. *Proc Nutr Soc* **61,**
954 203-215.

Rayman, MP (2004) The use of high-selenium yeast to raise selenium status: how does it measure up? *Br J Nutr* **92,** 557-573.

Rayman, MP (2008) Food-chain selenium and human health: emphasis on intake. *Br J Nutr* **100,** 254-268.

Rayman, MP, Abou-Shakra, FR, Ward, NI & Redman, CW (1996) Comparison of selenium levels in pre-eclamptic and normal pregnancies. *Biol Trace Elem Res* **55,** 9-20.

Rayman, MP, Bode, P & Redman, CW (2003) Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom. *Am J Obstet Gynecol* **189,** 1343-1349.

Redman, CW & Sargent, IL (2003) Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. *Placenta* **24 Suppl A,** S21-27.

Reilly, C (2006) *Selenium in food and health.* Springer, New York.

Reyes, H, Baez, ME, Gonzalez, MC, Hernandez, I, Palma, J, Ribalta, J, et al. (2000) Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals, in Chile. *J Hepatol* **32,** 542-549.

Roberts, JM & Lain, KY (2002) Recent Insights into the pathogenesis of pre-eclampsia. *Placenta* **23,** 359-372.

Robinson, MF, McKenzie, JM, Thomson, CD & van Rij, AL (1973) Metabolic balance of zinc, copper, cadmium, iron, molybdenum and selenium in young New Zealand women. *Br J Nutr* **30,** 195-205.

Roig, I, Garcia, R, Robles, P, Cortvrindt, R, Egozcue, J, Smitz, J, et al. (2006) Human fetal ovarian culture permits meiotic progression and chromosome pairing process. *Hum Reprod* **21,** 1359-1367.

Ross, C, Morriss, A, Khairy, M, Khalaf, Y, Braude, P, Coomarasamy, A, et al. (2010) A systematic review of the effect of oral antioxidants on male infertility. *Reprod Biomed Online*.

Rotruck, JT, Pope, AL, Ganther, HE, Swanson, AB, Hafeman, DG & Hoekstra, WG (1973) Selenium: biochemical role as a component of glutathione peroxidase. *Science* **179,** 588-590.

Roy, SK & Treacy, BJ (1993) Isolation and long-term culture of human preantral follicles. *Fertil Steril* **59,** 783-790.

Ruder, EH, Hartman, TJ & Goldman, MB (2009) Impact of oxidative stress on female fertility. *Curr Opin Obstet Gynecol* **21,** 219-222.

Rumiris, D, Purwosunu, Y, Wibowo, N, Farina, A & Sekizawa, A (2006) Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. *Hypertens Pregnancy* **25,** 241-253.

Safarinejad, MR & Safarinejad, S (2009) Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. *J Urol* **181,** 741-751.

Schwarz, K & Foltz, CM (1957) Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. *J. Am. Chem. Soc.* **79,** 3292-3293.

Scott, R, MacPherson, A, Yates, RW, Hussain, B & Dixon, J (1998) The effect of oral selenium supplementation on human sperm motility. *Br J Urol* **82,** 76-80.

Shennan, DB (1987) A study of selenate efflux from human placental microvillus membrane vesicles. *Biosci Rep* **7,** 675-680.

1001 Shennan, DB (1988) Selenium (selenate) transport by human placental brush border
1002 membrane vesicles. *Br J Nutr* **59,** 13-19.
1003 Sibai, B, Dekker, G & Kupferminc, M (2005) Pre-eclampsia. *Lancet* **365,** 785-799.
1004 Sievers, E, Arpe, T, Schleyerbach, U, Garbe-Schonberg, D & Schaub, J (2001) Plasma
1005 selenium in preterm and term infants during the first 12 months of life. *J Trace*
1006 *Elem Med Biol* **14,** 218-222.
1007 Smith, AM & Picciano, MF (1986) Evidence for increased selenium requirement for the
1008 rat during pregnancy and lactation. *J Nutr* **116,** 1068-1079.
1009 Steegers, EA, von Dadelszen, P, Duvekot, JJ & Pijnenborg, R (2010) Pre-eclampsia.
1010 *Lancet*.
1011 Steer, P (2005) The epidemiology of preterm labor--a global perspective. *J Perinat Med*
1012 **33,** 273-276.
1013 Strambi, M, Longini, M, Vezzosi, P, Berni, S & Buoni, S (2004) Selenium status, birth
1014 weight, and breast-feeding: pattern in the first month. *Biol Trace Elem Res* **99,** 71-
1015 81.
1016 Stuart, LD & Oehme, FW (1982) Environmental factors in bovine and porcine abortion.
1017 *Vet Hum Toxicol* **24,** 435-441.
1018 Sunde, RA (1990) Molecular biology of selenoproteins. *Annu Rev Nutr* **10,** 451-474.
1019 Surai, PF (2006) *Selenium in Nutrition and Health.* Nottingham University Press UK,
1020 Nottingham.
1021 Tan, M, Sheng, L, Qian, Y, Ge, Y, Wang, Y, Zhang, H, et al. (2001) Changes of serum
1022 selenium in pregnant women with gestational diabetes mellitus. *Biol Trace Elem*
1023 *Res* **83,** 231-237.
1024 Tara, F, Rayman, MP, Boskabadi, H, Ghayour-Mobarhan, M, Sahebkar, A, Yazarlu, O, et
1025 al. (2010) Selenium supplementation and premature (pre-labour) rupture of
1026 membranes: a randomised double-blind placebo-controlled trial. *J Obstet*
1027 *Gynaecol* **30,** 30-34.
1028 Thompson, JN, Erdody, P & Smith, DC (1975) Selenium content of food consumed by
1029 Canadians. *J Nutr* **105,** 274-277.
1030 Thomson, CD (2004) Assessment of requirements for selenium and adequacy of selenium
1031 status: a review. *Eur J Clin Nutr* **58,** 391-402.
1032 Thomson, CD & Robinson, MF (1986) Urinary and fecal excretions and absorption of a
1033 large supplement of selenium: superiority of selenate over selenite. *Am J Clin*
1034 *Nutr* **44,** 659-663.
1035 Thomson, CD, Robinson, MF, Butler, JA & Whanger, PD (1993) Long-term
1036 supplementation with selenate and selenomethionine: selenium and glutathione
1037 peroxidase (EC 1.11.1.9) in blood components of New Zealand women. *Br J Nutr*
1038 **69,** 577-588.
1039 Twomey, T, Crinion, RAP & Glazier, DB (1977) Selenium toxicity in cattle in Co.
1040 Meath. *Irish Veterinary Journal* **31,** 41-46.
1041 Ursini, F, Heim, S, Kiess, M, Maiorino, M, Roveri, A, Wissing, J, et al. (1999) Dual
1042 function of the selenoprotein PHGPx during sperm maturation. *Science* **285,**
1043 1393-1396.
1044 Van Dorst, SH & Peterson, PJ (1984) Selenium speciation in the soil solution and its
1045 relevance to plant uptake. *J. Sci. Food Agric.* **35,** 601-605.

1046 Van Vleet, JF (1980) Current knowledge of selenium-vitamin E deficiency in domestic
1047 animals. *J Am Vet Med Assoc* **176,** 321-325.
1048 Vanderlelie, J, Venardos, K, Clifton, VL, Gude, NM, Clarke, FM & Perkins, AV (2005)
1049 Increased biological oxidation and reduced anti-oxidant enzyme activity in pre-
1050 eclamptic placentae. *Placenta* **26,** 53-58.
1051 Voetsch, B, Jin, RC, Bierl, C, Benke, KS, Kenet, G, Simioni, P, et al. (2007a) Promoter
1052 polymorphisms in the plasma glutathione peroxidase (GPx-3) gene: a novel risk
1053 factor for arterial ischemic stroke among young adults and children. *Stroke* **38,** 41-
1054 49.
1055 Voetsch, B, Jin, RC, Bierl, C, Deus-Silva, L, Camargo, EC, Annichino-Bizacchi, JM, et
1056 al. (2007b) Role of Promoter Polymorphisms in the Plasma Glutathione
1057 Peroxidase (GPx-3) Gene as a Risk Factor for Cerebral Venous Thrombosis.
1058 *Stroke*.
1059 Wall, PD, Pressman, EK & Woods, JR, Jr. (2002) Preterm premature rupture of the
1060 membranes and antioxidants: the free radical connection. *J Perinat Med* **30,** 447-
1061 457.
1062 Walsh, SW & Wang, Y (1993) Deficient glutathione peroxidase activity in preeclampsia
1063 is associated with increased placental production of thromboxane and lipid
1064 peroxides. *Am J Obstet Gynecol* **169,** 1456-1461.
1065 Wang, Y & Walsh, SW (1996) Antioxidant activities and mRNA expression of
1066 superoxide dismutase, catalase, and glutathione peroxidase in normal and
1067 preeclamptic placentas. *J Soc Gynecol Investig* **3,** 179-184.
1068 Welsh, SO, Holden, JM, Wolf, WR & Levander, OA (1981) Selenium in self-selected
1069 diets of Maryland residents. *J Am Diet Assoc* **79,** 277-285.
1070 WHO/FAO/IAEA (1996) Trace Elements in Human Nutrition and Health. World Health
1071 Organisation, Geneva.
1072 Woods, JR, Jr. (2001) Reactive oxygen species and preterm premature rupture of
1073 membranes-a review. *Placenta* **22 Suppl A,** S38-44.
1074 Woods, JR, Jr., Plessinger, MA & Miller, RK (2001) Vitamins C and E: missing links in
1075 preventing preterm premature rupture of membranes? *Am J Obstet Gynecol* **185,**
1076 5-10.
1077 Wu, SH, Oldfield, JE, Whanger, PD & Weswig, PH (1973) Effect of selenium, vitamin E,
1078 and antioxidants on testicular function in rats. *Biol Reprod* **8,** 625-629.
1079 Yang, G & Zhou, R (1994) Further observations on the human maximum safe dietary
1080 selenium intake in a seleniferous area of China. *J Trace Elem Electrolytes Health*
1081 *Dis* **8,** 159-165.
1082 Yang, G, Zhou, R, Yin, S, Gu, L, Yan, B, Liu, Y, et al. (1989) Studies of safe maximal
1083 daily dietary selenium intake in a seleniferous area in China. I. Selenium intake
1084 and tissue selenium levels of the inhabitants. *J Trace Elem Electrolytes Health*
1085 *Dis* **3,** 77-87.
1086 Yang, GQ, GE, K, Chen, J & Chen, X (1988) Selenium-related endemic diseases and the
1087 daily selenium requirement of humans. *World Rev. Nutr. Diet* **55,** 98-152.
1088 Yang, GQ, Wang, SZ, Zhou, RH & Sun, SZ (1983) Endemic selenium intoxication of
1089 humans in China. *Am J Clin Nutr* **37,** 872-881.

1090 Ye, Y, Shibata, Y, Yun, C, Ron, D & Rapoport, TA (2004) A membrane protein complex
1091 mediates retro-translocation from the ER lumen into the cytosol. *Nature* **429,** 841-
1092 847.
1093 Yildirim, A, Altinkaynak, K, Aksoy, H, Sahin, YN & Akcay, F (2004) Plasma xanthine
1094 oxidase, superoxide dismutase and glutathione peroxidase activities and uric acid
1095 levels in severe and mild pre-eclampsia. *Cell Biochem Funct* **22,** 213-217.
1096 Zachara, BA, Dobrzynski, W, Trafikowska, U & Szymanski, W (2001) Blood selenium
1097 and glutathione peroxidases in miscarriage. *BJOG* **108,** 244-247.
1098 Zachara, BA, Mikolajczak, J & Trafikowska, U (1993a) Effect of various dietary
1099 selenium (Se) intakes on tissue Se levels and glutathione peroxidase activities in
1100 lambs. *Zentralbl Veterinarmed A* **40,** 310-318.
1101 Zachara, BA, Wardak, C, Didkowski, W, Maciag, A & Marchaluk, E (1993b) Changes in
1102 blood selenium and glutathione concentrations and glutathione peroxidase activity
1103 in human pregnancy. *Gynecol Obstet Invest* **35,** 12-17.
1104 Zadrozna, M, Gawlik, M, Nowak, B, Marcinek, A, Mrowiec, H, Walas, S, et al. (2009)
1105 Antioxidants activities and concentration of selenium, zinc and copper in preterm
1106 and IUGR human placentas. *J Trace Elem Med Biol* **23,** 144-148.
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Figure legends

Figure 1: Selenium metabolic pathway. This diagram illustrates how selenoproteins can be produced in the body from a variety of selenium sources. Glutathione (GSH) is considered to be the main component of the selenium metabolism pathway taking part in the first of a series of reduction reactions which convert selenite to hydrogen selenide (H_2Se). [Se]Met: selenomethionine; [Se]Cys: selenocysteine. Adapted from (Sunde, 1990, Ip, 1998, Patrick, 2004).

Figure 2: Major pathways of reactive oxygen species generation and metabolism. Superoxide can be generated by specialized enzymes, such as the xanthine or NADPH oxidases, or as a byproduct of cellular metabolism, particularly the mitochondrial electron transport chain. Superoxide dismutase (SOD) then converts the superoxide to hydrogen peroxide (H_2O_2) which has to be rapidly removed from the system. This is generally achieved by catalase or peroxidases, such as the selenium dependent glutathione peroxidases (GPxs) which use reduced glutathione (GSH) as the electron donor.