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**Selenium in reproductive health**

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

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4 **Short Title:** Selenium in reproductive Health

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24 **Abstract**25 Hiten D. Mistry PhD<sup>1</sup>, Fiona Broughton Pipkin DPhil<sup>2</sup>, Christopher W. G. Redman MD<sup>3</sup>26 & Lucilla Poston PhD<sup>1</sup>

27

28 Selenium is an essential trace element of importance to human biology and health.

29 Increasing evidence suggests that this mineral plays an important role in normal growth

30 and reproduction in animals and humans, and selenium supplementation is now

31 recommended as part of public health policy in geographical areas with severe selenium

32 deficiency in soil. Here, the biological functions of selenium are addressed prior to a

33 detailed review of associations between selenium status and reproductive health. In many

34 countries, selenium dietary intake falls below the recommended nutrient intakes (RNIs)

35 and is inadequate to support maximal expression of the selenoenzymes. Numerous reports

36 implicate selenium deficiency in several reproductive and obstetric complications

37 including male and female infertility, miscarriage, pre-eclampsia, fetal growth restriction,

38 preterm labour, gestational diabetes and obstetric cholestasis. Currently, there is

39 inadequate information from the available small intervention studies to inform public

40 health strategies. Larger intervention trials are required to reinforce or refute a beneficial

41 role of selenium supplementation in disorders of reproductive health.

42

43 **Keywords:** Antioxidant, pregnancy, reproduction, selenium

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## 47 **Introduction**

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

64

### 65 *Selenium, amino acids and selenoproteins*

66 The amino acids methionine and cysteine contain sulphur in the form of thiol groups.  
67 Selenium can replace the sulphur to form selenomethionine ([Se]Met) or selenocysteine  
68 ([Se]Cys or Sec) as a normal physiological process. A selenoprotein is any protein that  
69 includes a Sec or [Se]Met residue, which confers specific biological function. Dietary

70 selenium, initially taken up from the soil and concentrated by plants, is absorbed in the  
71 small intestine and incorporated into proteins by complex mechanisms which remain  
72 unclear (Reilly, 2006). The majority of selenium in the human diet is derived from  
73 [Se]Met in plant materials and both [Se]Met and Sec in animal products (Combs, 2001,  
74 Sunde, 1990). [Se]Met cannot be synthesised by higher animals, including humans, but  
75 after ingestion is non-specifically incorporated into proteins (e.g. haemoglobin, albumin)  
76 in place of methionine (Thomson et al., 1993). Selenophosphate is synthesised from  
77 selenide and ATP through the action of selenophosphate synthetase 2 (*SEPHS2*) and is  
78 the source of selenium from which Sec is then formed and co-translationally incorporated  
79 into selenoproteins at in-frame UGA codons. Sec has a lower  $pK_a$  than Cys and is more  
80 nucleophilic, so is more reactive. During protein catabolism, Sec is rapidly broken down  
81 to elemental selenium, leaving no free pool of cellular Sec. This has a biological  
82 advantage, since Sec can react with oxygen, thioredoxin and thioredoxin reductase,  
83 giving rise to rapid NADPH oxidation and the formation of damaging reactive oxygen  
84 species (ROS) (Lu and Holmgren, 2009).

85

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

93 leads to higher selenium content of proteins in the form of [Se]Met and Sec (Kohrle et al.,  
94 2005).

95

96 Selenite ( $\text{SeO}_3^{2-}$ ; inorganic form of selenium) crosses the plasma membrane, and reacts  
97 with cytoplasmic thiols in the reduction pathway; this forms selenide, which is then  
98 methylated, giving rise to methylated selenium derivatives that are excreted in urine, in  
99 expired air via the lungs and in faeces (Fig. 1) (Sunde, 1990, Ip, 1998). In humans these  
100 products of selenium metabolism are predominantly excreted in urine (Yang et al., 1989,  
101 Oster and Prellwitz, 1990). The proportion of selenium intake excreted in this manner  
102 depends on dietary intakes; when this is high, urinary excretion will also be high and vice  
103 versa (Robinson et al., 1973, Thomson and Robinson, 1986, Oster and Prellwitz, 1990).

104

105 There appears to be no homeostatic control of selenium absorption, which is unusual, in  
106 contrast, for example, to the complex regulation of iodine absorption (Kohrle et al., 2005,  
107 Reilly, 2006, Fairweather-Tait et al., 2010). Selenium is stored in the tissues in varying  
108 density: 30% in the liver, 30% in muscle, 15% in the kidney, 10% in the plasma, and the  
109 remaining 15% throughout other organs (Levander, 1987, Reilly, 2006). Concentrations  
110 of free selenium are greatest in the renal cortex and pituitary gland, followed by the  
111 thyroid gland, adrenals, testes, ovaries, liver, spleen, and cerebral cortex (Drasch et al.,  
112 2000, Kohrle et al., 2005).

113

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

116 (Beckett and Arthur, 2005, Thomson, 2004), in part because they have powerful  
117 antioxidant functions. The selenoenzymes have a Sec group at their active sites, which  
118 enables the formation of disulphide bonds (Burk and Levander, 2006); these function as a  
119 redox centre, participating in transfer of electrons between molecules (Flohe et al., 2000).  
120 Of the identified selenoproteins, three are iodothyronine deiodinases, which catalyse the  
121 removal of iodine from the 5 or 5' positions of iodothyronine substrates. This regulates  
122 the activation and inactivation of thyroid hormones in all tissues (Beckett and Arthur,  
123 2005). A further three are the thioredoxin reductase family (TrxR1, TrxR2 and TrxR3).  
124 Their substrates, thioredoxin and thioredoxin peroxidase do not contain selenium. These  
125 constitute a powerful dithiol-disulphide system that regulates the cellular redox state (Hill  
126 et al., 2003, Burk et al., 2003, Mostert et al., 2003) (Table 1). The Trx system also  
127 regulates other antioxidants (such as heme oxygenase-1, methionine sulphoxide  
128 reductases, ascorbate (Vit C), tocopherol (Vit E), ubiquinone (Q10)), modulates several  
129 transcription factors (eg those involved in the maturation of p53) and regulates apoptosis  
130 and protein phosphorylation (Surai, 2006, Arner, 2009, Mostert et al., 2003).  
131  
132 Of particular importance to reproduction and pregnancy are the 6 antioxidant GPxs which  
133 play a pivotal role in reducing hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and lipid peroxides to harmless  
134 products (water and alcohols; Fig. 2), thereby dampening the propagation of damaging  
135 ROS (Rotruck et al., 1973, Brigelius-Flohe et al., 2003). This important pathway of  
136 cellular protection has been demonstrated in all mammalian tissue examined (Allan et al.,  
137 1999, Knapen et al., 1999). As antioxidants, the GPxs help maintain membrane integrity,  
138 protect prostacylin production, and limit the propagation of oxidative damage to lipids,



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

149

#### 150 *Dietary selenium*

151 Plant foods are the major dietary sources of selenium in most countries (Rayman, 2000,  
152 Combs, 2001). Surveys suggest that wheat is the most efficient selenium accumulator of  
153 the common cereals, and is one of the most important selenium sources for man (Lyons et  
154 al., 2003, Reilly, 2006). The content in food depends on the selenium content of the soil  
155 where plants are grown or animals are raised. For example, the selenium content in the  
156 soil of the high plains of northern Nebraska and the Dakotas is very high, and the  
157 inhabitants have the highest selenium intakes in the US (Longnecker et al., 1991).  
158 Whether this degree of high intake has any positive health benefit is not known, but toxic  
159 effects supervene when intake exceeds ~ 850 µg/day (Goldhaber, 2003).

160

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

166

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

175

176 In addition, in wetter regions, rain leaches selenium from the soil (Reilly, 2006).

177 Selenium forms both inorganic and organic compounds and can be an oxidant as well as a  
178 reductant, an important factor in soil formation (Van Dorst and Peterson, 1984).

179 Selenium's chemical adaptability accounts for its widespread occurrence in soils, plants,  
180 animals and humans (Bauer, 1997). Soil selenium concentrations range from 0.1 to more  
181 than 100 mg/Kg. However, most soils contain between 1.0 to 1.5 mg/Kg (0.1-0.6 mg/Kg  
182 is considered deficient) (Lyons et al., 2003, Combs, 2001).

183

184 *Selenium deficiency*

185 The optimal range of selenium intake to ensure biological benefit appears to be narrow  
186 and has still not been determined with certainty; however selenium deficiency has been  
187 studied in animals and humans (Van Vleet, 1980, Zachara et al., 1993a, Hurst et al.,  
188 2010). Selenium deficiency as assessed by dietary intake and/or blood selenium  
189 concentrations has been identified in people inhabiting geographical regions notable for  
190 low soil selenium content, such as volcanic regions and in Finland and New Zealand,  
191 where the reported average selenium intake is approximately 30-40  $\mu\text{g}/\text{day}$  (Levander and  
192 Burk, 1994, Thomson, 2004). Animal selenium deficiency diseases have been routinely  
193 identified since the 1950s in livestock in countries that have low selenium soil conditions  
194 (Oldfield, 1997, Koller and Exon, 1986).

195

196 Human selenium deficiency diseases have been recognised in China and Tibet (Moreno-  
197 Reyes et al., 2003, Levander and Beck, 1997). Keshan disease, a reversible endemic  
198 cardiomyopathy, is characterised by focal myocardial necrosis often associated with  
199 inflammatory infiltrates and calcification. The disorder is exclusively endemic in  
200 selenium-deficient rural areas of China e.g. Keshan (Beck et al., 2003) and  
201 supplementation with selenium tablets (as sodium selenite) in pregnancy (Moore et al.,  
202 2000) provides highly effective protection against its development in susceptible women  
203 (Beck et al., 2003).

204

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

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

213

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

220

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

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

235

236 Selenium intake appears on average to be at or above the RDA in the US or Canada. A  
237 study in Maryland in 1981 reported that adults consumed an average of 81 µg/day of  
238 selenium (Welsh et al., 1981) and recently this has been estimated to be 108 µg/day for  
239 all US adults and 89 µg/day for women (Chun et al., 2010). A Canadian survey in 1975  
240 reported intakes of 113 to 220 µg/day (Thompson et al., 1975); this was followed in 1998  
241 by a report indicating consumption of between 98-224 µg/day (Gissel-Nielsen, 1998).  
242 Conversely, the UK selenium dietary intake is generally below the RNI; a dietary survey  
243 published by the UK Government over the period 1994 to 1995 indicated that the average  
244 intake was as low as 30–40 µg per day (Ministry Of Agriculture Fisheries and Food,  
245 1997) a figure which had not improved in a survey conducted between 2008 and 2009  
246 (Department of Health, 2009). Although it has been argued that UK intakes are  
247 sufficiently low to warrant government intervention (Rayman, 2000), a UK government  
248 expert committee concluded in 1998 that intervention was, at that time, not warranted  
249 (Department of Health, 1998). Whether, this conclusion pertains to the dietary intake in  
250 2010 is uncertain and is worthy of investigation.

251 *Selenium toxicity*

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

265

### 266 **Selenium in Reproductive Health**

267 The role that selenium plays in both male and female reproduction is well recognised in  
268 animal husbandry (Reilly, 2006). Selenium is essential for male fertility, being required  
269 for testosterone biosynthesis and the formation and normal development of spermatozoa  
270 (Behne et al., 1996, Flohe, 2007). Studies using selenoprotein P-knockout mice support a  
271 requirement for selenium in testicular function (Hill et al., 2003) and animals fed  
272 selenium-deficient diets show impaired spermatozoan motility with flagellar defects  
273 localised primarily to the midpiece, decreasing the chance of fertilisation (Behne et al.,  
274 1996, Wu et al., 1973).

275

276 Testicular tissue contains high concentrations of selenium, predominantly as GPx4 and  
277 this provides the pivotal link between selenium, sperm quality and male fertility since  
278 GPx4 is a fundamental determinant of the architecture of the spermatozoan midpiece  
279 (Beckett and Arthur, 2005, Knapen et al., 1999), and is considered to shield developing  
280 sperm cells from oxidative DNA damage (Ursini et al., 1999, Safarinejad and Safarinejad,  
281 2009). ROS have been implicated in male infertility because, through attack of the  
282 spermatozoa membrane, sperm viability is decreased.

283

284 Some evidence suggests that increasing selenium dietary intake increases antioxidant  
285 GPx activity, thereby increasing male fertility (Irvine, 1996). Bleau *et al's* study in 1984  
286 was one of the first indications, in humans, that selenium deficiency may be related to  
287 male fertility, reporting an optimal range between 50 - 60 µg/ml in semen and a positive  
288 correlation between sperm count and semen selenium concentration in 125 men from  
289 couples being investigated for infertility (Bleau et al., 1984). In Scotland (where mean  
290 selenium intakes are below requirements, ~30-40 µg per day) a placebo-controlled  
291 randomised control trial (RCT) of 64 men demonstrated that sperm quality and fertility  
292 improved after selenium supplementation (Scott et al., 1998). A placebo-controlled RCT  
293 from Tunisia of 54 infertile and 54 men on placebo also demonstrated the beneficial  
294 effects of a combination of vitamin E (400 mg) and selenium (225 µg) daily supplements  
295 for 3 months on improving sperm motility (Keskes-Ammar et al., 2003). In another recent  
296 placebo-controlled RCT in Iran of 468 infertile men, supplementation with 200 µg  
297 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



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

322

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

329

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

334

### 335 **Selenium and disorders of pregnancy**

#### 336 *Miscarriage*

337 Miscarriage, a clinically detectable pregnancy that fails to progress past 24 weeks'  
338 gestation, occurs in 10-20% of all pregnancies (Bradley and Hamilton-Fairley, 1998).

339 Genetic (chromosomal) abnormalities explain at least half of all miscarriages. Although  
340 anatomical, endocrine, immune, infective and thrombophilic conditions are other possible  
341 causes, most chromosomally normal miscarriages remain unexplained or idiopathic  
342 (Hirschfeld et al., 2007).

343

344 Miscarriages have been associated with selenium deficiency in veterinary practice (Stuart  
345 and Oehme, 1982), and selenium supplements prevent early pregnancy loss in sheep  
346 (Hidiroglou, 1979). In humans, a UK observational study reported significantly lower  
347 serum selenium concentrations in 40 women with 1<sup>st</sup> trimester miscarriage compared to  
348 40 age-matched non-pregnant and 40 healthy gestation-matched women (Barrington et  
349 al., 1996). A similar finding was reported in another observational study from Turkey of  
350 20 women with 1<sup>st</sup> trimester miscarriage compared to controls (Kocak et al., 1999). Red-  
351 cell and hair selenium concentrations are also reported to be lower in women with  
352 recurrent miscarriage (Al-Kunani et al., 2001, Kumar et al., 2002). Early pregnancy loss  
353 has been linked to reduced antioxidant protection of biological membranes and DNA and  
354 also to low concentrations of the selenium-dependent GPx (Barrington et al., 1997,  
355 Zachara et al., 2001, Jauniaux et al., 2006), and although speculative, women with  
356 recurrent pregnancy loss could potentially benefit from optimisation of selenium status.

357

### 358 *Normal Pregnancy*

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

365

366 In countries such as Poland and Yugoslavia where soil selenium content and dietary  
367 intake are low, maternal selenium concentrations and GPx activity fall during pregnancy,  
368 being the lowest at delivery compared with non-pregnant controls (Mihailovic et al.,  
369 2000, Zachara et al., 1993b). In contrast, in areas of very high soil selenium content e.g.  
370 South Dakota, it would appear that there is no gestational trend in serum selenium  
371 concentrations (Kundu et al., 1985). Babies generally have lower selenium concentrations  
372 compared to the mother (Gathwala et al., 2000, Mistry et al., 2008), which might be  
373 anticipated as selenium is transported via the placenta across a concentration gradient via  
374 an anion exchange pathway, (Shennan, 1987, Shennan, 1988).

375

376

### 377 *Pre-eclampsia*

378 Pre-eclampsia (*de novo* proteinuric hypertension) is estimated to occur in ~3% of all  
379 pregnancies and is a leading cause of maternal and perinatal mortality and morbidity in  
380 the Western world (Sibai et al., 2005, Steegers et al., 2010); together with other  
381 hypertensive disorders of pregnancy, pre-eclampsia is responsible for approximately  
382 60,000 maternal deaths each year (Broughton Pipkin, 2001) and increases perinatal  
383 mortality five-fold (Roberts and Lain, 2002). Optimal outcome for the mother and child  
384 often dictates that the infant is delivered early leading to increased preterm delivery and  
385 low infant birthweight rates. Placental and maternal systemic oxidative stress are  
386 components of the syndrome (Poston, 2004) and contribute to a generalised maternal  
387 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/cc3/projects/cc3\\_eclampsia.shtml](http://www.wtccc.org.uk/cc3/projects/cc3_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 3<sup>rd</sup> 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

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

466

467 Some small studies have attempted to assess the influence of selenium supplementation  
468 on the incidence of pregnancy related hypertensive disorders, Han *et al.*, conducted a  
469 small placebo-controlled RCT in Beijing, China, a population with a high risk of  
470 pregnancy-induced hypertension (PIH) and between 26%-27% and selenium deficiency.  
471 52 women with known risk factors for PIH were randomised to selenium (100 µg/day)  
472 for 6-8 weeks during late pregnancy, and 48 were randomised to placebo (Han and Zhou,  
473 1994). The selenium supplemented group had a reduced incidence of development of PIH  
474 (7.7%; 4/52) compared to the placebo group (22.7%; 11/48), and significantly increased  
475 maternal and cord blood selenium concentrations. Another very small prospective  
476 double-blind, placebo-controlled RCT study in Indonesia, reported lower rates of pre-  
477 eclampsia and/or PIH in women who were at increased risk of developing these  
478 conditions, after supplementation (n = 29) with a range of antioxidants and cofactors  
479 including selenium (100 µg) (Rumiris et al., 2006). Neither study adequately addressed

480 the role of supplementation on the incidence of pre-eclampsia. Recently however, Tara *et*  
481 *al*, investigated selenium supplementation of Iranian women in their first trimester (100  
482 µg selenium per day) in a small pilot RCT and concluded that supplementation may be  
483 associated with a lower frequency of pre-eclampsia although this didn't quite reach  
484 statistical significance (Tara et al., 2010).

485

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

500

501

502 *Preterm labour*



503 Preterm labour (labour < 37 weeks' gestation) is a major cause of perinatal morbidity and  
504 mortality occurring in 6-7% pregnancies in the developed world and up to 25% in  
505 undeveloped countries (Steer, 2005) and is likely to be of complex origin. Amongst the  
506 few studies to have investigated selenium and preterm labour, Dobrzynski *et al* from  
507 Poland reported lower maternal selenium concentrations and reduced maternal and cord  
508 plasma GPx activities in 46 women who delivered preterm compared to 42 women  
509 delivering at term (Dobrzynski et al., 1998). The low selenium concentrations and GPx  
510 activities in the blood of the preterm infants were proposed to contribute to respiratory  
511 distress syndrome, retinopathy of prematurity, increased haemolysis or other prematurity  
512 related conditions (Dobrzynski et al., 1998). A study from Germany of formula-fed  
513 preterm infants (gestational age < 32 weeks, birthweight < 1500 g) observed significantly  
514 lower mean plasma selenium concentrations compared to healthy term infants who were  
515 also formula-fed (Sievers et al., 2001). Another recent report from Iran of 30 preterm  
516 (gestational age <34 weeks) and 30 term infants (gestation age >37 weeks) also revealed  
517 significantly lower serum selenium concentrations in the preterm infants compared to  
518 term controls (Iranpour et al., 2009). A study from the USA of 13 preterm and 15 term  
519 infants found no differences in maternal plasma selenium concentrations, but also  
520 reported that preterm infants had lower selenium concentrations compared to term infants  
521 (Mask and Lane, 1993). As might be anticipated, the daily dietary selenium intake was 2-  
522 3 times higher (96-134 µg) than in the subjects reported in the Polish population  
523 (Dobrzynski et al., 1998). Evidently, population selenium intake may explain some  
524 variation between studies.  
525

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

540

#### 541 *Fetal growth restriction*

542 Fetal growth restriction or delivery of a small for gestational age infant (SGA) is defined  
543 as an individualised birthweight ratio below the 10<sup>th</sup> percentile, and is associated with  
544 increased perinatal mortality and morbidity (Cetin et al., 2004). Some studies of SGA  
545 deliveries report a reduced placental selenium concentrations (Klapec et al., 2008),  
546 whereas others report higher (Osada et al., 2002, Zadrozna et al., 2009) or unchanged  
547 concentrations (Llanos and Ronco, 2009). Strambi *et al.*, demonstrated that in 81 SGA  
548 (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

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

580

#### 581 *Gestational diabetes mellitus*

582 Gestational diabetes mellitus (GDM) is one of the more common diseases in pregnancy,  
583 affecting between 2% and 5% of pregnant women and is associated with birthweights  
584 above the 90<sup>th</sup> centile, increased levels of primary Caesarean deliveries and neonatal  
585 hypoglycaemia (Gilmartin et al., 2008). GDM is defined as a deficient insulin supply  
586 relative to the increased demands that are characteristic of pregnancy (Metzger et al.,  
587 2007). The causes are not known but are closely related to a constitutional risk of type 2  
588 diabetes in later life and strongly associated with obesity. A significant proportion of  
589 GDM women develop type 2 diabetes 5-16 years after pregnancy (17-63% risk) (Kjos et  
590 al., 1995, O'Sullivan and Mahan, 1964, Mestman et al., 1972).

591

592 A link between selenium and glucose metabolism has been observed previously in animal  
593 studies (Becker et al., 1996, McNeill et al., 1991, Ezaki, 1990) and selenium administered  
594 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**

618 There are wide differences in selenium intake across diverse populations, depending on  
619 the selenium content of the soil, and hence the selenium content in staple foodstuffs, as  
620 well as on variations in individuals' diets. Both deficiency and excess are damaging to  
621 health. In turn, varying intakes are associated with differences in selenoprotein and  
622 selenoenzyme expression in different tissues. This must be taken into account when  
623 comparing data from different countries or populations. Evidently, the balance between  
624 intake, tissue concentration and selenoenzyme synthesis is a very delicate one. This  
625 review illustrates the potential influence that selenium status has on many disorders  
626 relating to both animal and human reproduction and pregnancy. While persuasive  
627 evidence already exists to suggest that additional selenium would be beneficial in some of  
628 these disorders, results from intervention trials underway or planned have the potential to  
629 reinforce or refute the argument for increasing selenium intake.

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1110 **Figure legends**

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1112 **Figure 1:** Selenium metabolic pathway. This diagram illustrates how selenoproteins can  
1113 be produced in the body from a variety of selenium sources. Glutathione (GSH) is  
1114 considered to be the main component of the selenium metabolism pathway taking part in  
1115 the first of a series of reduction reactions which convert selenite to hydrogen selenide  
1116 ( $\text{H}_2\text{Se}$ ). [Se]Met: selenomethionine; [Se]Cys: selenocysteine. Adapted from (Sunde,  
1117 1990, Ip, 1998, Patrick, 2004).

1118

1119 **Figure 2:** Major pathways of reactive oxygen species generation and metabolism.  
1120 Superoxide can be generated by specialized enzymes, such as the xanthine or NADPH  
1121 oxidases, or as a byproduct of cellular metabolism, particularly the mitochondrial electron  
1122 transport chain. Superoxide dismutase (SOD) then converts the superoxide to hydrogen  
1123 peroxide ( $\text{H}_2\text{O}_2$ ) which has to be rapidly removed from the system. This is generally  
1124 achieved by catalase or peroxidases, such as the selenium dependent glutathione  
1125 peroxidases (GPxs) which use reduced glutathione (GSH) as the electron donor.