

Review Article

The possible role of selenium status in adverse pregnancy outcomes

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Abstract

The present study reviews the possible role of Se status during pregnancy regarding adverse pregnancy outcomes, with emphasis on those related to diminished antioxidant activity and increased oxidative stress. Studies have reported that Se could play an important role in adverse outcomes such as miscarriages, neural tube defects, diaphragmatic hernia, premature birth, low birth weight, pre-eclampsia, glucose intolerance and gestational diabetes. Also, low Se status has been associated with adverse outcomes among HIV-infected pregnant women and their offspring. Nevertheless, the function of Se in the aetiology of pregnancy complications is yet to be elucidated. Available evidence presents the following limitations: most study designs do not allow conclusions about causal relationships; study populations, selection of subjects, research setting, procedures for defining sample size and analytical methods are often poorly described; many studies fail to adjust for important confounding variables. In addition, population studies assessing the relationship between Se intake during pregnancy and health outcomes are scarce. Further research is still needed to clarify the role of Se status in adverse pregnancy outcomes, especially those related to augmented oxidative stress.

Key words: Selenium: Pregnancy: Pregnancy complications: Oxidative stress

It is well recognised that maternal nutritional conditions during pregnancy can have a profound and long-lasting effect not only on women's health status but also on fetal, newborn and infant health, development and well-being^(1–3).

During pregnancy, there can be a reduction in maternal Se concentrations, regardless of whether there are any gestational complications^(4–9). Such reduction could be explained by haemodilution caused by maternal plasma expansion^(10,11), or it could reflect transport of Se to the fetus⁽¹¹⁾. It has also been hypothesised that during this period, higher amounts of Se are used for producing antioxidant compounds such as glutathione peroxidase (GPx) and selenoprotein P⁽¹²⁾.

Se, a mineral with well-known antioxidant activity that participates in the synthesis of selenoproteins, such as GPx, selenoprotein P and thioredoxin reductase, could have an

important role in pregnancy, especially because oxidative stress might be increased during this period^(13–17). Consequently, antioxidant defences have a central role in modulating events mediated by oxidative stress and could be related to perinatal morbidity and mortality^(18–22).

In addition, an extensive body of literature has suggested that exacerbated oxidative stress during pregnancy plays an important role in many diseases and adverse pregnancy outcomes, which include miscarriages, pre-eclampsia, gestational diabetes, premature rupture of membranes and intra-uterine growth restriction^(16,22–31).

Thus, the objective of the present review is to discuss the possible role of Se status during pregnancy regarding adverse pregnancy outcomes, with emphasis on those related to diminished antioxidant activity and increased oxidative stress.

Abbreviation: GPx, glutathione peroxidase.

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Selenium status and adverse fetal and perinatal outcomes

Barrington *et al.*⁽³²⁾ observed significantly lower serum Se levels among women who had had a miscarriage in the first trimester of pregnancy than in either pregnant women or non-pregnant healthy volunteers. The authors referred that haemodilution cannot explain the difference in Se levels between these groups, considering that serum albumin and total protein concentrations of the pregnant and miscarried groups were not different. They suggested that low Se status in women with miscarriage could be related to membrane and cell DNA damage caused by loss of the antioxidant activity performed by Se.

Similar results were found by Al-Kunani *et al.*⁽³³⁾, who described significantly lower hair Se concentrations in women with recurrent miscarriages when compared with non-pregnant women who had had successful pregnancies. In disagreement is the study carried out by Zachara *et al.*⁽³⁴⁾, who observed no significant differences in whole-blood and plasma Se levels when comparing women with miscarriage against women with normal pregnancies. Nevertheless, these authors found that women with miscarriage had significantly lower erythrocyte and plasma GPx activities than women with normal pregnancies and non-pregnant women.

Reduced Se concentrations also seem to be related to neural tube defects, as reported in some studies. Güvenç *et al.*⁽³⁵⁾ observed low Se status in both mothers and their infants with neural tube defects and suggested that the occurrence of such defects could be related not only to a deficiency of the mineral, but also to inadequate intakes.

Although mechanisms implicated in the prevention of neural tube defects are still unknown, Martin *et al.*⁽³⁶⁾ suggested that in women with low Se status, low levels of folate could worsen oxidative stress, and thus purine and pyrimidine synthesis could be jeopardised.

Cengiz *et al.*⁽³⁷⁾ and Zeyrek *et al.*⁽³⁸⁾ assessed multiple micronutrients in mothers and their newborns with neural tube defects and found conflicting results regarding Se status. The first study found statistically significant lower maternal Se levels among cases. The second study, on the other hand, found that Se concentrations did not differ between cases and controls. It has also been reported in the literature that low Se intake could be associated with the occurrence of diaphragmatic hernia. Although this finding is supported by a large population-based case-control study⁽³⁹⁾, the authors highlight limitations which include the use of a FFQ for the assessment of nutrient adequacy and the fact that maternal levels of nutrients were not measured. In addition, associations might have been exclusive to a particular nutrient or a consequence of highly correlated nutrients, and because of the elevated number of nutrients investigated, some might have shown statistically significant differences by chance. It is also possible that lack of information from non-participants might have biased the results.

Low Se status could also be related to adverse perinatal outcomes. It has been suggested that newborn Se concentrations may be related to the Se status of their mothers^(30,40,41), and that pre-term infants born to healthy

women have lower Se concentrations than do term newborns^(41–44). Such findings are not surprising since shortened gestations hinder appropriate transport of Se from the mother to the fetus. In fact, Al-Saleh *et al.*⁽⁴²⁾ emphasised that pre-term newborns can be at risk of Se deficiency, especially if total parenteral nutrition is needed. Moreover, as a consequence of their lower Se status, pre-term infants might have their antioxidant defences impaired, especially with respect to GPx activity, a Se-dependent enzyme, which may be related to higher incidence of oxygen dependence at 28 d of life^(44,45). There are conflicting results, however, regarding the influence of gestational age on Se concentrations and erythrocyte GPx activity^(30,46,47).

Dobrzynski *et al.*⁽³⁰⁾ have considered a possible relationship between low Se status and premature birth, since pre-term parturient women in their study had lower plasma and blood Se concentrations than did term parturient women and healthy non-pregnant women. In their study, no significant correlations between gestational age and Se status measures were found. The authors also reported that pre-term parturient women had significantly lower antioxidant status when compared with their controls, as indicated by their erythrocyte GPx activity. Nonetheless, this relationship is not supported by other studies^(41,47).

With regard to the relationship between Se status and birth weight, there is still much disagreement in the literature. Although many studies have pointed to a possible association^(11,41,42,47,48), significant results varied according to the groups included or excluded from the analyses or the type of statistical tests applied. For instance, Iranpour *et al.*⁽⁴¹⁾ observed only significant correlations between cord blood Se levels and birth weight when pre-term and term infants were considered together in the analysis; Al-Saleh *et al.*⁽⁴²⁾ found only a significant correlation between newborn Se concentrations and birth weight when low-birth-weight infants were included in the analysis; Kaplec *et al.*⁽⁴⁸⁾ found a significant correlation between placental Se concentrations and birth weight among newborns whose birth weight was appropriate for gestational age, but not among intra-uterine growth-restricted newborns; Bogden *et al.*⁽⁴⁷⁾ found no significant correlation between birth weight and serum Se as continuous variables, but a significant association was observed when the lowest decile of Se level was compared with the nine highest. In addition, many authors have failed to establish any kind of relationship between Se status and birth weight^(30,46,49). Bogden *et al.*⁽⁴⁷⁾ suggested that conflicting findings could be partly attributed to different timing in blood collection (i.e. early in pregnancy or at delivery), and that the effect of prematurity on birth weight could mask the association between Se levels and birth weight.

Concerning intra-uterine growth restriction, Zadrozna *et al.*⁽⁵⁰⁾ found increased Se concentrations in complicated placentas, suggesting a physiological response to maintain GPx activity due to augmented oxidative stress. On the other hand, Kaplec *et al.*⁽⁴⁸⁾ observed that Se levels were not predictors of intra-uterine growth restriction. Their findings are consistent with those of Llanos & Ronco⁽⁵¹⁾, who did not report statistically significant differences between

Table 1. Main characteristics and results of studies assessing the relationship between selenium status and adverse fetal outcomes

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Barrington <i>et al.</i> ⁽³²⁾	CS	South Wales, UK	To assess the association between Se deficiency and first-trimester miscarriage	Forty women presenting first-trimester miscarriage and not classified as recurrent miscarriers, forty age-matched healthy non-pregnant women and forty pregnant women in the first trimester of gestation	Healthy pregnant women had significantly lower serum Se concentrations than non-pregnant women ($P < 0.0001$; 95% CI 0.104, 0.283 $\mu\text{mol/l}$). Women who miscarried in the first trimester had significantly lower serum Se concentrations ($P = 0.0054$) when compared with normal pregnant women (95% CI 0.041, 0.227 $\mu\text{mol/l}$)
Al-Kunani <i>et al.</i> ⁽³³⁾	CC	Hull, UK	To evaluate the relationship between Se levels in women's blood and hair and the risk of recurrent miscarriages	Twenty-six non-pregnant women with history of three successive miscarriages and eighteen non-pregnant controls with no history of miscarriages and having given birth to a healthy baby within the previous year	Hair Se concentrations were significantly lower in women with recurrent miscarriage when compared with their non-pregnant controls ($P < 0.001$), although no differences were found for serum Se levels (95% CI between means - 0.03, 0.01)
Zachara <i>et al.</i> ⁽³⁴⁾	CS	Bydgoszcz, Poland	To determine whole-blood and plasma Se levels, erythrocyte glutathione concentrations and erythrocyte and plasma GPx activities in women with first- and second-trimester miscarriage	Forty women with miscarriage (seventeen in the first trimester and twenty-three in the second trimester of pregnancy), thirty-six pregnant women and twenty-eight healthy age-matched non-pregnant women	Whole-blood and plasma mean Se levels were not statistically different between women who miscarried and women with normal pregnancies. There were statistically significant differences when both groups were compared with non-pregnant women (whole blood: $P < 0.0001$; plasma: $P < 0.001$). Erythrocyte and plasma GPx activities were significantly lower in women who miscarried when compared with both pregnant ($P < 0.01$ and 0.001 , respectively) and non-pregnant women ($P < 0.001$ and 0.0001 , respectively)
Güvenç <i>et al.</i> ⁽³⁵⁾	CS	Elazığ, Turkey	To investigate the relationship between maternal and neonatal Se status and the occurrence of NTD	Twenty-eight newborns with NTD, thirty-two mothers and their newborns following healthy pregnancies, in addition to twenty healthy non-pregnant women	Maternal serum and hair Se concentrations were significantly lower in those whose babies had NTD compared with women with normal pregnancies ($P < 0.02$) and healthy non-pregnant women ($P < 0.001$) Both serum and hair Se concentrations of infants with NTD were significantly lower than those of normal newborns ($P < 0.01$ and $P < 0.001$ for serum and hair concentrations, respectively)
Martin <i>et al.</i> ⁽³⁶⁾	CC	Palma de Mallorca, Spain	To determine aminothiols and Se status and to analyse thiolic status and amino acids involved in arginine synthesis in the case of Se depletion and repletion, investigating their association with the occurrence of NTD	Forty-four women who had been pregnant with an NTD child (cases), and 181 women who had at least two healthy children, who had never taken periconceptional folic acid nor had prior history of congenital malformations, abortions and obstetric complication (controls)	The NTD group had significantly lower median serum Se levels compared with controls ($P < 0.001$) When compared with controls, women with depleted Se who had conceived fetuses with NTD had significantly higher plasma cysteine concentrations ($P = 0.01$), total cysteine: total homocysteine ratio ($P < 0.001$), glutathione ($P = 0.005$) and arginine concentrations ($P = 0.004$)
Cengiz <i>et al.</i> ⁽³⁷⁾	CC	Ankara, Turkey	To assess maternal Zn, Se, Cu and Pb concentrations in women who had a second-trimester diagnosis of NTD	Fourteen women whose pregnancies were terminated after a second-trimester diagnosis of NTD (cases) and fourteen age-, gravidity- and socio-economic status-matched women with normal fetal outcome (controls)	Serum Se levels were significantly lower in women whose babies had NTD when compared with women with normal pregnancies ($P < 0.001$). A statistically significant positive correlation was found between Zn and Se ($r = 0.676$; $P < 0.001$) and a negative correlation between Zn, Se and Cu ($r = 0.425$ and -0.443 ; $P < 0.05$)
Zeyrek <i>et al.</i> ⁽³⁸⁾	CC	Sanliurfa, Turkey	To investigate a possible relationship between serum folic acid, vitamin B ₁₂ , Zn, Cu, Se and Pb levels and the occurrence of NTD	Seventy-four newborns with NTD and seventy healthy infants born in the same period from a similar socio-economic group and their mothers	Umbilical cord and maternal serum Se levels in samples collected within 30 min after birth did not differ significantly between the two groups
Yang <i>et al.</i> ⁽³⁹⁾	CC	USA	To investigate the association of maternal nutrient intake, including Se, with the risk of congenital diaphragmatic hernia in their offspring	Data on 297 congenital diaphragmatic hernia cases and 4982 controls collected from population-based birth defects surveillance systems from the eight states participating in the National Birth Defects Prevention Study	Adjusted OR was 1.7 (95% CI 1.1, 2.6) for lower percentile intakes of Se

CS, cross-sectional; CC, case-control; GPx, glutathione peroxidase; NTD, neural tube defect.

Table 2. Main characteristics and results of studies assessing the relationship between selenium status and adverse perinatal outcomes

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Kantola <i>et al.</i> ⁽¹¹⁾	CS	Finland (Kuopio and Helsinki), Russia (St Petersburg) and Estonia (Tallinn and Rakvere)	To assess Se levels in maternal blood and placenta, as well as in cord blood, and their impact on Cd, Zn and Cu levels in the first and third trimesters of pregnancy	Serum and blood samples were collected from 216 mothers (152 immediately before or after delivery and sixty-four before abortion) and hair samples from 128 mothers. In addition, 181 placental samples were collected (132 from healthy babies and forty-nine from healthy abortion patients)	Among Finish smokers, placental Se levels were significantly higher in the first trimester than at term ($P < 0.001$). Among non-smokers, placental, serum and whole-blood Se levels were significantly higher in the first trimester ($P < 0.001$ for placental Se; $P < 0.05$ for serum Se; $P < 0.01$ for whole-blood Se) Serum and cord blood Se levels in non-smoking Finnish mothers were negatively and positively, respectively, correlated with newborn's birth weight ($P < 0.005$)
Dobrzynski <i>et al.</i> ⁽³⁰⁾	CS	Bydgoszcz, Poland	To measure Se and glutathione concentrations and GPx activity in blood components of pregnant women and cord blood components of their newborns, as well as placental Se levels, comparing term and pre-term deliveries	Forty-two TPW, forty-six PPW and their infants, and thirty-four healthy NPW	Plasma Se concentrations were significantly lower in TPW compared with NPW ($P < 0.01$) PPW showed whole-blood and plasma Se concentrations significantly lower than did TPW ($0.01 < P < 0.02$) and NPW ($0.001 < P < 0.01$). PPW had erythrocyte GPx activity significantly lower than NPW ($P < 0.05$). Whole-blood and plasma Se concentrations were significantly lower in umbilical cord of pre-term babies compared with umbilical cord of babies at term ($P < 0.01$).
Al-Saleh <i>et al.</i> ⁽⁴²⁾	CS	Al-Kharj, Saudi Arabia	To evaluate Se status of newborns and serum Se concentrations in their umbilical cord blood	300 Newborns given birth after uncomplicated pregnancies	PB had significantly lower serum Se concentrations when compared with full-term infants ($P < 0.0002$). There was a weak but significant correlation between newborn Se concentrations and birth weight ($r = 0.1568$; $P = 0.007$). However, when low-birth-weight newborns were excluded from analysis, no correlation was found
Iranpour <i>et al.</i> ⁽⁴¹⁾	CS	Isfahan, Iran	To compare maternal and umbilical cord blood Se levels in TB and PB	Thirty TB (gestational age > 37 weeks) and thirty PB (gestational age < 37 weeks) and their mothers	Mean Se concentrations were significantly lower in PB compared with TB ($P = 0.0001$), but no statistically significant difference was found when their mothers were compared ($P = 0.15$). Maternal and cord blood Se concentrations were correlated in the TB group ($r = 0.56$; $P = 0.001$), but not in the PB group ($r = 0.20$; $P = 0.26$) Cord blood Se levels and birth weight were not correlated either in the TB ($r = -0.13$; $P = 0.48$) or PB groups ($r = 0.01$; $P = 0.93$), although when data of all infants were considered together, there was a significant correlation ($r = 0.59$; $P < 0.0001$)
Galinier <i>et al.</i> ⁽⁴³⁾	CS	Toulouse Cedex, France	To report neonatal reference ranges for ten relevant analytes, including Se, according to gestational age	510 Infants whose birth weight was appropriate for gestational age	Cord blood Se concentrations were significantly lower in premature than in term neonates ($P < 0.001$)
Nassi <i>et al.</i> ⁽⁴⁴⁾	L*	Florence, Italy	To assess antioxidant protection and its relationship with the levels of antioxidant enzymes and nutritional status of their constitutive trace elements (Se, Zn and Cu) in PB with ELBW	Thirty PB with ELBW and thirty healthy TB	Until 20 d of life, both erythrocyte GPx activity and erythrocyte Se levels were significantly lower in PB with ELBW infants compared with healthy TB ($P < 0.05$). Plasma Se levels were not significantly different when groups were compared at any of the time points considered

Table 2. Continued

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Mentro <i>et al.</i> ⁽⁴⁵⁾	L*	Salt Lake City, UT, USA	To examine the relationship between Se status of extremely PB and Se intake, gestational age and oxygen dependence at weeks 1 and 4 of life	Eighteen PB (≤ 30 weeks of gestation) who experienced respiratory distress requiring mechanical ventilation during the first 48–72 h of life	Erythrocyte GPx activities were directly related to gestational age of infants, and the lowest activities were found in most PB at both weeks 1 (r 0.665; $P=0.01$) and 4 (r 0.567; $P=0.05$). Lower erythrocyte GPx activities at week 4 were related to a greater incidence of oxygen dependence at 28 d of life (r - 0.730; $P=0.01$)
Makhoul <i>et al.</i> ⁽⁴⁶⁾	CS	Haifa, Israel	To determine serum Se concentrations in the umbilical cord of neonates born between 24 and 42 weeks of gestation; to measure maternal serum Se concentrations at birth; to assess the possible effects of maternal disease during gestation on serum Se concentrations in maternal and umbilical cord blood	168 Pregnant women between 24 and 42 weeks of gestation and their newborn infants	Although umbilical cord serum Se concentrations were significantly correlated with birth weight (r 0.237; $P=0.002$) and 5 min Apgar score (r 0.202; $P<0.01$), multiple regression analysis showed that only gestational age was significantly associated with umbilical cord serum Se concentration ($P=0.012$). There was a significant negative correlation between maternal-umbilical Se difference and birth weight (r - 0.369; $P<0.0001$) and gestational age (r - 0.337; $P<0.0001$)
Bodgen <i>et al.</i> ⁽⁴⁷⁾	NCC	Camden, NJ, USA	To examine whether low dietary Se, low serum Se and/or low erythrocyte GPx in early pregnancy are predictors of fetal prematurity and low birth weight; to assess whether adverse effects of Se on pregnancy outcomes were related to thyroid function	107 Poor healthy pregnant women with pre-term delivery (< 37 weeks of gestation) were selected as cases. Among these, twenty-five women delivered very pre-term (< 32 completed weeks of gestation) and eighty-two delivered moderately pre-term (≥ 32 to < 37 completed weeks of gestation). Controls were 126 women randomly selected from the 829 pregnant women who delivered at term assisted in the same clinics	Serum Se concentrations did not differ between cases and controls. When pregnant women with Se concentrations in the lowest decile were compared with those with higher concentrations, lower Se in early pregnancy predicted lower birth weight for all subjects combined and for full-term controls ($P=0.01$ and $P=0.02$, respectively) Serum Se and erythrocyte GPx concentrations were not significantly different when subjects were categorised by gestational age at delivery, among other variables There were no significant differences in serum Se between women with gestational diabetes, pregnancy-induced hypertension or pre-eclampsia when compared with women without complications
Klapec <i>et al.</i> ⁽⁴⁸⁾	CS	Osijek, Croatia	To investigate whether placental Se, Cd and Pb levels were related to fetal growth in a group of pregnancies with birth weight appropriate for gestational age and in a group of IUGR cases	Placental samples collected from healthy mother–newborn pairs. Eighty-five samples were assessed: forty-nine IUGR and thirty-six appropriate-for-gestational age births	Placental Se content was associated with birth weight in the group whose birth weight was appropriate for gestational age ($P<0.05$)
Odland <i>et al.</i> ⁽⁴⁹⁾	CS	Russia (Nikel, Monchegorsk and Arkhangelsk) and Norway (Kirkenes, Hammerfest and Bergen)	To compare Cu, Fe, Se and Zn serum concentrations of delivering women; to evaluate the influence of maternal status of these elements on birth weight and BMI of the child	151 Delivering women living in north-western Russia and 167 delivering women living in northern and southern Norway	None of the essential trace elements assessed, which included Se, was a significant predictor of birth weight, even if the model was adjusted for gestational age. Serum Se was a significant positive predictor of neonate's BMI ($P=0.003$)
Zadrozna <i>et al.</i> ⁽⁵⁰⁾	CS	Kraków, Poland	To assess changes in antioxidant activities and Cu, Zn and Se concentrations in pre-term and term placentas, as well as in placentas from pregnancies complicated by IUGR	Eight normal full-term pregnancy human placentas, six IUGR term complicated pregnancy human placentas and six pre-term pregnancy human placentas (34–37 weeks of gestational age)	Se concentrations were significantly increased in IUGR and pre-term placentas compared with control placentas ($P<0.05$). Such an increase could have increased GPx activity at a level comparable with control placentas

Table 2. Continued

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Llanos & Ronco ⁽⁵¹⁾	CS	Santiago, Chile	To measure essential metals (Zn, Fe, Cu and Se) and toxicants (Cd, Ar, Pb and Hg), together with both oxidative stress parameters and antioxidant enzymatic activities, in placentas of mothers delivering neonates with normal and low birth weight at term	Twenty placentas of neonates with fetal growth restriction and twenty placentas of normal-birth-weight neonates, both groups delivered at term	Placental Se concentrations and GPx activity did not differ statistically between normal-weight neonates and neonates with fetal growth restriction
Kupka <i>et al.</i> ⁽⁵²⁾	L*	Dar es Salaam, Tanzania	To determine the association between Se status during pregnancy and pregnancy outcomes, mother-to-child transmission of HIV and child mortality	670 AIDS-free, HIV-infected pregnant women recruited between 12 and 27 weeks of gestation	Low plasma Se levels were associated with increased risks of fetal death ($P=0.02$), child death ($P=0.03$) and HIV transmission through the intra-partum route ($P=0.03$). Low Se status was not associated with risks of low birth weight ($P=0.22$) or pre-term birth ($P=0.51$) but was associated with an apparently lower risk of small-for-gestational age ($P=0.03$)

CS, cross-sectional; GPx, glutathione peroxidase; TPW, term parturient women; PPW, pre-term parturient women; NPW, non-pregnant women; TB, term babies; L*, longitudinal (including cohort and follow-up studies); ELBW, extremely low birth weight; NCC, nested case-control; LUGR, intra-uterine growth restriction.

normal-weight neonates and neonates with fetal growth restriction.

The occurrence of adverse outcomes among infants born to HIV-infected mothers might be influenced by maternal Se status: low status has been associated with increased risks of fetal and child deaths, as well as intra-partum and breast-feeding transmission of HIV and lower risk of small-for-gestational age infants. Kupka *et al.*⁽⁵²⁾ have cited the role of Se in antioxidant defences as one of the factors that might be implicated in fetal deaths. Later, the same group conducted a randomised, double-blind, placebo-controlled trial of Se supplementation to HIV-infected pregnant women and found that the intervention reduced the risk of infant death after 6 weeks, although no significant effects were found regarding the risks of low birth weight, pre-term birth and small-for-gestational age⁽⁵³⁾.

The main characteristics of studies assessing the relationship between Se status and the occurrence of adverse fetal outcomes are shown in Table 1, whereas Table 2 summarises the characteristics of studies which investigated the relationship between Se status and adverse perinatal outcomes.

Selenium status and adverse maternal outcomes

There is evidence that maternal plasma Se concentrations are reduced in the presence of pre-eclampsia^(54,55). Lower Se levels have been reported in the amniotic fluid of pre-eclamptic pregnant women compared with their normotensive controls⁽⁵⁶⁾ and infants born to pre-eclamptic women have shown lower umbilical cord blood Se levels than infants born to normotensive pregnant women⁽⁵⁵⁾. Decreased GPx activity has also been observed in pre-eclamptic pregnancies⁽⁵⁵⁾. Rayman *et al.*⁽⁵⁷⁾ suggested that Se deficiency before the onset of pre-eclampsia might be related to the incidence of the disease, although they speculated that the same association might not be found in populations with adequate Se status. Despite the body of evidence pointing to an association between Se status and pre-eclampsia, some studies have failed to find the same results^(58–60).

Not only can serum Se levels be reduced in the presence of abnormal glucose metabolism and gestational diabetes^(6,61,62), but inadequate dietary Se intake has also been related to these conditions. Bo *et al.*⁽⁶¹⁾ reported significantly lower Se intake in hyperglycaemic pregnant women, even after adjustment for confounders such as age, gestational age, familial diabetes, pre-pregnancy BMI and total energy intake. However, associations between maternal Se levels and outcomes such as the percentages of caesarean sections, small- or large-for-gestational age newborns, pre-term births and neonatal morbidities have not been found. Taking these results into account, Kilinc *et al.*⁽⁶²⁾ suggested that Se status is important to glucose-intolerant individuals, and that its deficiency could aggravate diabetes and be related to complications in the gestational period. In addition, Bo *et al.*⁽⁶¹⁾ proposed that dietary counselling and antioxidant supplementation might be useful if further research confirms the relationship between micronutrient status and hyperglycaemia.

Finally, low Se status of HIV-infected pregnant women has been related to increased risk of mortality, whereas high Se

Table 3. Main characteristics and results of studies assessing the relationship between selenium status and adverse maternal outcomes

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Tan <i>et al.</i> ⁽⁶⁾	CS	Shanghai, China	To assess and compare changes in serum Se concentrations in HPW, pregnant women with impaired glucose tolerance and GD along with their gestational period	Ninety-eight pregnant women with impaired glucose tolerance, forty-six pregnant women with GD, ninety HPW and seventeen age-matched healthy NPW	Serum Se levels were significantly lower in HPW compared with NPW ($P < 0.001$). Women at more advanced gestational ages had lower serum Se levels for both normal and glucose intolerant and diabetic pregnant women ($P < 0.05$ for both groups). Both impaired glucose tolerance and GD groups had significantly lower serum Se concentrations compared with normal pregnant women and NPW ($P < 0.001$ for all comparisons)
Atamer <i>et al.</i> ⁽⁵³⁾	CS	Diyarbakir, Turkey	To assess changes in erythrocyte superoxide dismutase, catalase and placental GPx activities; to measure serum malondialdehyde, Cu, Zn, Se, leptin and placental malondialdehyde and GSH	Thirty-two pre-eclamptic pregnant women, twenty-eight HPW and twenty-five healthy NPW	Serum Se levels were significantly lower in pre-eclamptic women compared with both HPW and NPW ($P < 0.001$). Placental GPx activity was significantly lower in pre-eclamptic women than in HPW ($P < 0.001$)
Mistry <i>et al.</i> ⁽⁵⁴⁾	CS	Nottingham, UK	To examine Se concentration and GPx expression and activity levels and markers of oxidative stress on maternal and umbilical venous blood samples or the placenta from HPW, pre-eclamptic women and healthy age-matched NPW	Twenty-five white pre-eclamptic women, twenty-seven white HPW attending prenatal care and twenty-two white healthy age-matched NPW	There were significant trends for decreasing both plasma Se concentrations and plasma GPx activity from NPW to HPW and pre-eclamptic women ($P < 0.001$) Umbilical venous Se concentrations and plasma GPx activity were also significantly reduced in the samples from babies born to pre-eclamptic mothers when compared with the ones born to normotensive mothers ($P < 0.005$ and $P < 0.02$, respectively). Reduced placental GPx activity was observed in pre-eclampsia placenta compared with normal pregnancy ($P < 0.001$)
Dawson <i>et al.</i> ⁽⁵⁵⁾	CS	Galveston, TX, USA	To determine changes in metal levels in third-trimester amniotic fluid and changes in metal levels associated with pre-eclampsia	130 Amniotic fluid samples collected from forty-eight normal and ten pre-eclamptic pregnant women between 33 and 36 weeks of gestation and from fifty-three normal and nineteen pre-eclamptic pregnant women from 37 to 40 weeks of gestation	Se levels were 30% lower in the presence of pre-eclampsia in early third-trimester pregnancies ($P < 0.02$). However, no significant difference was found for late third-trimester pregnancies
Rayman <i>et al.</i> ⁽⁵⁶⁾	CC	Oxford, UK	To investigate the association between low Se status and increased risk of pre-eclampsia	Fifty-three pre-eclamptic obstetric patients and fifty-three pregnant controls	Pre-eclamptic women had significantly lower median Se concentrations compared with their controls ($P < 0.001$). Women in the bottom tertile of toenail Se levels had a greater incidence of pre-eclampsia (OR 4.4, 95% CI 1.6, 14.9). Pre-eclamptic women who gave birth before 32 weeks of gestation had significantly lower Se status than those who delivered after 32 weeks ($P = 0.029$)
Roy <i>et al.</i> ⁽⁵⁷⁾	CS	Singapore	To assess amniotic fluid Se levels in pre-eclamptic women and in HPW	Amniotic fluid samples from forty pre-eclamptic women between 34 and 42 weeks of gestation and amniotic fluid samples from sixty HPW	Amniotic fluid Se levels did not differ significantly between HPW and pre-eclamptic pregnancies

Table 3. Continued

Author	Study design	Place	Objective(s)	Population/material characteristics and sample size	Main results as reported by the authors
Poranen <i>et al.</i> ⁽⁵⁸⁾	CS	Turku, Finland	To measure lipid peroxidation products and antioxidant function in maternal serum and placental tissue in normal and pre-eclamptic pregnancies	Fifteen pre-eclamptic human placentas and fifteen uncomplicated pregnancy human placentas collected at 29–41 gestational weeks. Maternal serum from both groups was obtained before delivery at 28–41 gestational weeks	No statistically significant difference in GPx between pre-eclamptic and normal placentas was found ($P=0.249$)
Mahomed <i>et al.</i> ⁽⁵⁹⁾	CC	Harare, Zimbabwe	To assess the risk of pre-eclampsia in relation to post-partum maternal leucocyte Se, Zn and Cu concentrations	Thirty-three parturient women with eclampsia, 138 parturient women with pre-eclampsia (cases) and 191 parturient women whose pregnancies were not complicated by pregnancy-induced hypertension (controls)	Pre-eclamptic women had higher median leucocyte Se concentration compared with controls ($P<0.001$). The risk of pre-eclampsia increased significantly across increasing quartiles of maternal leucocyte Se (adjusted OR 3.38 for the highest quartile, 95% CI 1.53, 7.45, adjusted P for linear trend risk = 0.002)
Bo <i>et al.</i> ⁽⁶⁰⁾	L*	Turin, Italy	To assess dietary intake of antioxidants (including vitamins, Zn and Se); to evaluate Zn and Se serum levels in pregnant women with different degrees of gestational hyperglycaemia; to verify whether antioxidants were independent predictors of gestational hyperglycaemia	In a first cohort, 126 women with GD and eighty-four women with one abnormal glucose tolerance test (cases) and 294 pregnant women with normal glucose tolerance (controls). In a second cohort, seventy-one hyperglycaemic pregnant women (forty-two with abnormal glucose tolerance and twenty-nine with GD – cases) and 123 normoglycaemic pregnant women (control)	There was a negative association between Se dietary intake and gestational hyperglycaemia (OR 0.97, 95% CI 0.95, 0.99). Serum Se levels were also negatively associated with gestational hyperglycaemia (OR 0.92, 95% CI 0.87, 0.95)
Kilinc <i>et al.</i> ⁽⁶¹⁾	CS	Kahramanmaras, Turkey	To investigate the association between serum Se levels in pregnant women with GD, with GI and glucose-tolerant pregnant women	178 Pregnant women between 24 and 28 weeks of gestation were divided into three groups: thirty pregnant women with an abnormal 50 g and abnormal 100 g oral glucose tolerance test; forty-seven pregnant women with an abnormal 50 g oral glucose tolerance test but a normal 100 g oral glucose tolerance test; 101 pregnant women with a normal 50 g glucose tolerance test	Serum Se levels were significantly lower in women with GD and GI compared with their controls with normal glucose tolerance ($P<0.001$)
Kupka <i>et al.</i> ⁽⁶²⁾	L*	Dar es Salaam, Tanzania	To investigate the association between Se status and HIV disease progression among pregnant women	949 HIV-infected pregnant women recruited between 12 and 27 weeks of gestation	Plasma Se levels were inversely related to the risk of maternal mortality (adjusted $P=0.01$). Although high plasma Se levels were not protective for progression to CD4 cell count < 200 cells/mm ³ , higher Se levels were associated with higher CD4 cell count in the first year of follow-up. In later years of follow-up, the apparent benefit baseline Se levels disappeared, as presented graphically

CS, cross-sectional; CC, case-control; GD, gestational diabetes; GI, glucose intolerance; GPx, glutathione peroxidase; HPW, healthy pregnant women; L*, longitudinal (including cohort and follow-up studies); NPW, non-pregnant women.

status has been associated with higher CD4 cell count in the first years of follow-up in the cohort study by Kupka *et al.*⁽⁶³⁾. However, in the Se supplementation study conducted by the same group and previously cited in the present paper, the intervention had no statistically significant effects on CD4, CD8 and CD3 cell counts, viral load or maternal mortality⁽⁵³⁾.

The main characteristics of studies assessing the relationship between low Se status and adverse maternal outcomes are presented in Table 3.

Limitations of available evidence

It must be emphasised that the role of Se status in the aetiology of pregnancy complications is yet to be established. Although a connection between low Se status and the occurrence of adverse fetal outcomes has been suggested, because most available studies are cross-sectional or case-control, their results are not appropriate to the assessment of causal relationships. Thus, low Se status could either be implicated in the causal process of such adverse outcomes or simply indicate a maternal physiological response to increased oxidative stress states. Ideally, high-quality prospective studies assessing the Se status of women through the periconceptional period to pregnancy loss or detection of any adverse outcome should be carried out, but such type of design is not always feasible.

Additionally, some studies have limitations that should be noted and addressed in future research, which comprise a comprehensive description of study populations (including their Se status), selection of subjects, research setting and analytical methods poorly described. The lack of such type of information limits generalisation of study results. Also, most studies fail to present the procedures for defining sample sizes, thus making it difficult to judge their statistical power, especially because many studies have small sample sizes.

Among important confounding variables, which should be taken into account but are not frequently assessed, are maternal Se intake, parity and smoking habits. Maternal nutrient intake assessment as a whole is essential since it can also be hypothesised that Se-deficient women lack other micronutrients, and thus Se deficiency itself might not explain adverse fetal outcomes. Indeed, Bogden *et al.*⁽⁴⁷⁾ suggested that the association between serum Se and birth weight in neonates could simply reflect good maternal nutritional status. Parity could contribute not only to low Se status but also to other micronutrient deficiencies, which could also influence pregnancy outcomes. Smoking should also be included in the analyses since it induces oxidative stress and consequently activates antioxidant defence mechanisms^(11,47). In addition, cigarettes might contain Se, which could also interfere in maternal Se status. Bogden *et al.*⁽⁴⁷⁾ highlighted the fact that most studies do not control for this variable, which can hinder possible associations between Se measurements and pregnancy outcomes.

Finally, even though there is evidence suggesting that Se status might be important in relation to the occurrence of gestational morbidities, large representative population studies assessing the relationship between Se intake during

pregnancy and maternal and newborn health outcomes are still scarce.

Conclusion

Although Se status might play an important role in adverse pregnancy outcomes, probably because of its participation in the antioxidant defence system as GPx, not enough evidence has been produced so far to form a comprehensive understanding of the role of Se. Further research with bigger sample sizes, prospective designs and well-documented reports are still needed, allowing greater statistical power and more robust analyses. Ideally, maternal Se and antioxidant status should be assessed from periconceptional through post-natal periods, and a large array of maternal and newborn outcomes should be addressed. Moreover, studies evaluating the relationship between dietary and supplementary Se intake before and during pregnancy in relation to adverse outcomes would be of great importance.

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