No effect of modest selenium supplementation on insulin resistance in UK pregnant women, as assessed by plasma adiponectin concentration

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Abstract
Concern has been expressed recently that Se may increase the risk of type 2 diabetes, but this has not been tested in a randomised-controlled trial (RCT) in pregnant women. We took advantage of having stored plasma samples from the Se in Pregnancy Intervention (SPRINT) RCT of Se supplementation in pregnancy to test the effect of Se supplementation on a marker of insulin resistance in UK pregnant women. Because our blood samples were not fasted, we measured plasma adiponectin concentration, a recognised marker of insulin resistance that gives valid measurements in non-fasted samples, as diurnal variability is minor and there is no noticeable effect of food intake. In SPRINT, 230 primiparous UK women were randomised to treatment with Se (60 μg/d) or placebo from 12 weeks of gestation until delivery. We hypothesised that supplementation with Se at a nutritional level would not exacerbate the fall in adiponectin concentration that occurs in normal pregnancy, indicating the lack of an adverse effect on insulin resistance. Indeed, there was no significant difference between the two groups in the change in adiponectin from 12 to 35 weeks (P = 0.938), nor when the analysis was restricted to the bottom or top quartiles of baseline whole-blood Se (P = 0.515 and 0.858, respectively). Cross-sectionally, adiponectin concentration was not associated with any parameter of Se status, either at 12 or 35 weeks. It is reassuring that a nutritional dose of Se had no adverse effect on the concentration of adiponectin, a biomarker of insulin resistance, in pregnant women of modest Se status.

Key words: Selenium: Pregnancy: Adiponectin: Diabetes: Insulin resistance

Concern has been expressed in recent years that Se may increase the risk of type 2 diabetes (T2D), and indeed a number of studies have implicated the selenoproteins, cytosolic glutathione peroxidase 1 (GPx1) and selenoprotein P1 (SEPP1) in insulin resistance1–4. However, epidemiological data are conflicting. Although higher Se status has been associated with higher prevalence of T2D or fasting plasma glucose in five cross-sectional studies, three such studies have found the opposite association and two have found no association1,5–7. Results of longitudinal or prospective studies have not supported a causal role for Se in T2D1,8. With regard to trial evidence, five randomised-controlled trials (RCT) with Se as a single agent reported on the risk of T2D, although none had T2D as a primary end point1,8,9. Of these, only one showed an increased incidence of T2D in the Se arm, although only in participants in the top tertile of plasma Se at baseline10.

Studies on pregnant women are also contradictory; in pregnant women without gestational diabetes (GDM), activity of the cytosolic selenoenzyme, GPx1, in erythrocytes increased during pregnancy and was positively associated with fasting plasma glucose, plasma insulin, C-peptide and the homoeostasis model of assessment for insulin resistance (HOMA-IR) index, suggesting an adverse effect of Se, or at least a selenoprotein11. By contrast, the literature also shows that pregnant women with impaired glucose tolerance or GDM have much lower serum Se concentrations than women with normal pregnancies12–14 and that there is an inverse relationship between serum Se and blood glucose concentration14. Furthermore, in a small group of pregnant women, the increase in plasma glucose following an oral glucose tolerance test administered at 12 weeks of gestation was inversely correlated with plasma Se concentration15. Recently, an RCT of Se (200 μg/d) in seventy women who had already developed GDM found a significant reduction in fasting plasma glucose, serum insulin and HOMA-IR in those on Se16. However, to date, there

Abbreviations: GDM, gestational diabetes; GPx3, glutathione peroxidise 3; RCT, randomised-controlled trial; SEPP1, selenoprotein P1; T2D, type 2 diabetes.

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has been no RCT of the effect of Se supplementation on the risk of GDM or insulin resistance in normal pregnant women. We took advantage of having stored plasma samples from the Se in Pregnancy Intervention (SPRINT) RCT of Se supplementation in pregnancy to test the effect of Se supplementation on a marker of insulin resistance in UK pregnant women(17). SPRINT was set up to assess the effect of Se supplementation on the risk of pre-eclampsia in pregnant women of low-to-moderate Se status(17). Although we could not validly measure plasma glucose or insulin as we only had non-fasted samples, we were able to measure plasma adiponectin, a recognised marker of insulin resistance(18) and a strong independent predictor of the risk of GDM and T2D(19–24). Adiponectin measurements are valid even in non-fasted plasma samples, as diurnal variability is minor and there is no noticeable effect of food intake(19,20,25,26). Higher plasma adiponectin concentration is associated with lower risk(20).

Adiponectin concentration falls substantially during the course of normal pregnancy(27). We hypothesised that supplementation with Se at a nutritional level would not exacerbate that fall, indicating a lack of an adverse effect of Se on insulin resistance. On the basis of our previous findings(17), we speculated that Se supplementation might even lessen the fall in plasma adiponectin in women in the bottom quartile of Se status at baseline.

**Methods**

**Participants**

Blood and plasma samples for this study originate from the SPRINT study (trial registration ISRCTN37927591, [http://controlledtrials.com/ISRCTN37927591](http://controlledtrials.com/ISRCTN37927591)), which randomised 230 primiparous women in Oxford, UK, to treatment with Se (60 μg/d Se, as Se yeast) or placebo (placebo yeast) from their first hospital antenatal visit (mean gestational age 12.3 weeks) until delivery of the baby(17). Blood samples, from which plasma was prepared, were collected at baseline (12 weeks), 20 and 35 weeks(17).

Five women were excluded from the analysis: one woman was recruited in error (treated with thyroxine), two had diabetes before conception and two were outliers, one with respect to whole-blood Se and one with respect to adiponectin concentration. One woman had no remaining plasma for adiponectin analysis at 12 weeks. There were 111 women in the placebo group and 113 in the Se group at baseline, and 107 in the placebo group and 104 in the Se group at 35 weeks (see Participant Flow chart in previous publication(17)).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. All procedures involving human subjects were approved by the Milton Keynes Research Ethics Committee (REC reference no. 08/H0603/46). A non-substantial amendment for additional laboratory measurements in stored samples was approved by NRES Committee South Central, Berkshire (27 July 2011). Written informed consent was obtained from all subjects.

**Anthropometric measurements**

Weight at 12 and 35 weeks was measured to the nearest 0·1 kg while subjects were dressed in light clothing. Subjects stood barefoot while height was measured to the nearest 0·01 m by using a wall-mounted stadiometer (Holtain Ltd). BMI was calculated using weight (kg) divided by height squared (m²).

**Laboratory analyses**

Whole-blood Se and plasma glutathione peroxidase 3 (GPx3) activity at 12 and 35 weeks were determined by inductively coupled plasma MS and a spectrophotometric assay, respectively, as previously described(17,28). The CV for the whole-blood Se assay was 0·25 % at 1·4 mmol/l and 0·17 % at 3·0 mmol/l(29). For GPx3, the inter-assay variation was 0·45 % and the intra-assay variation was 1·25 % (29).

Toenail Se at 16 weeks was measured using instrumental neutron activation analysis at the Interfaculty Reactor Institute in Delft, as previously described(17,30). The laboratory has an embedded quality-control system for quality assurance and management, which complies with the requirements of the International Standard ISO/IEC 17025:2005 and has been accredited by the Dutch Council for Accreditation since 1993.

 Plasma SEPP1 concentration at 35 weeks was measured by ELISA in the laboratory of Raymond Burk, as previously described(17,30). For quality control, each ELISA was run with two standards: purified SEPP1 and a standard plasma sample(31).

Total plasma adiponectin concentration at 12 and 35 weeks was measured using a commercial ELISA kit (Quantikine®, Human Total Adiponectin/Acrp30 Immunoassay; R&D Systems Europe Ltd) according to the manufacturer’s instructions ([http://www.rndsystems.com/pdf/drp300.pdf](http://www.rndsystems.com/pdf/drp300.pdf)). The intra- and inter-assay CV were 2·5 and 6·8 %, respectively.

**Statistical methods**

To use parametric analysis, adiponectin concentration was transformed using the natural logarithm (ln) to approximate a normal distribution. Then, the difference at baseline between placebo and Se groups was tested by an independent samples t test. A paired samples t test was used to compare adiponectin concentrations at 12 and 35 weeks within placebo and Se groups.

**Intention-to-treat analysis.** The difference in the change in adiponectin between placebo and Se groups from 12 to 35 weeks was tested by the Mann–Whitney U test. On the basis of effects seen previously in this study in women in the bottom Se status quartile (whole-blood Se)(17), we repeated the test in the group of women in the bottom quartile of whole-blood Se at baseline. Because a previous study saw adverse effects only in those in the top tertile of baseline plasma Se(19), we also carried out the same analysis in those of high status – that is, women in the top quartile in the current study. We also explored the difference in adiponectin concentration between placebo and Se groups at 35 weeks by ANCOVA, by adjusting for baseline ln-adiponectin concentration, as adiponectin concentration at baseline and 35 weeks were highly correlated (r 0·755; P < 0·001).

For the sample size per treatment group and an uncorrected two-sided significance level of 0·05, the trial had 80 % power to detect a 25 % difference in adiponectin change during pregnancy between Se and placebo groups.
Cross-sectional associations. To evaluate the cross-sectional associations between Se status and adiponectin concentration at baseline (12 weeks), we divided the population into quartiles by the various Se status parameters. The median value of each quartile was used as an ordinal variable to test the significance of the linear trend across quartiles by multiple linear regression analysis. Adjustment was made for baseline BMI, as BMI is known to be associated with adiponectin concentration(23) as was also the case in our study. No adjustment was made for gestational age despite the fact that it affects adiponectin concentration(27), as the range of gestational ages was very narrow (median 12 (interquartile range (IQR) 12, 13) weeks).

As the magnitude and range of both Se status and adiponectin concentration changed substantially over the course of the trial, we carried out a cross-sectional analysis at 35 weeks, stratified by treatment group. In-transformed adiponectin concentration at 35 weeks was adjusted for baseline ln-transformed adiponectin and BMI at 35 weeks.

Statistical analyses were conducted using IBM SPSS Statistics version 20. P-values < 0.05 (two-tailed) were considered significant.

Table 1. Baseline adiponectin concentrations in the group overall and in selenium and placebo groups separately, and P value for comparison between groups (Medians and interquartile ranges (IQR); geometric means and 95 % confidence intervals)

<table>
<thead>
<tr>
<th>Adiponectin concentrations (mg/l)</th>
<th>Overall</th>
<th>Se group</th>
<th>Placebo group</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>224</td>
<td>113</td>
<td>111</td>
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<tr>
<td>Median</td>
<td>12-51</td>
<td>12-90</td>
<td>11-11</td>
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<tr>
<td>IQR</td>
<td>8-90, 16-54</td>
<td>9-69, 16-54</td>
<td>7-93, 16-67</td>
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<tr>
<td>Mean</td>
<td>11-76</td>
<td>12-37</td>
<td>11-18</td>
<td>0.088</td>
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<tr>
<td>95 % CI</td>
<td>11-10, 12-47</td>
<td>11-39, 13-41</td>
<td>10-30, 12-13</td>
<td></td>
</tr>
</tbody>
</table>

* P value for difference between Se and placebo groups by independent samples t test.

Results

Baseline characteristics

Table 1 shows the baseline adiponectin concentrations in the group overall and in Se and placebo groups separately, and the P value for comparison between the groups. There was no significant difference in adiponectin concentration between treatment groups at baseline. We previously reported the lack of any significant difference in parameters of Se status (whole-blood Se, GPx3 activity, toenail Se) and other participant characteristics (age, ethnicity, gestational age, smoking, drinking, BMI) between treatment groups at baseline(27,28).

Effect of treatment

At 35 weeks, median whole-blood Se in the Se group was significantly higher than in the placebo group (1.87 (IQR 1.67, 2.15) v. 1.16 (IQR 1.05, 1.30) μmol/l, P < 0.001), although there was no significant difference in GPx3 activity between the two groups (P=0.140). Compared with baseline, in the women...
Table 3. Cross-sectional association between selenium status parameters and adiponectin concentration at baseline (12 weeks) (Geometric means and 95% confidence intervals; medians and interquartile ranges (IQR)).

<table>
<thead>
<tr>
<th>Se status parameters</th>
<th>Variables</th>
<th>First</th>
<th>Mean</th>
<th>95% CI</th>
<th>Second</th>
<th>Mean</th>
<th>95% CI</th>
<th>Third</th>
<th>Mean</th>
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<th>Mean</th>
<th>95% CI</th>
<th>P_{trend}</th>
</tr>
</thead>
<tbody>
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<td>Whole-blood Se</td>
<td>Participants (n)</td>
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<td>57</td>
<td>54</td>
<td>53</td>
<td>57</td>
<td>55</td>
<td>56</td>
<td>56</td>
<td>0.252</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Median (μmo/l)</td>
<td>108</td>
<td>0.84, 1.16</td>
<td>125</td>
<td>1.19, 1.31</td>
<td>139</td>
<td>1.32, 1.16</td>
<td>1.61</td>
<td>1.47, 2.26</td>
<td>0.026</td>
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<tr>
<td></td>
<td>Adiponectin conc.</td>
<td>11.35</td>
<td>10.13, 12.71</td>
<td>11.81</td>
<td>10.53, 13.24</td>
<td>11.34</td>
<td>10.08, 12.75</td>
<td>12.69</td>
<td>11.23, 14.12</td>
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<td></td>
<td>(mg/l)</td>
<td>54</td>
<td>58</td>
<td>57</td>
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<td>54</td>
<td>57</td>
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<tr>
<td>GPx3</td>
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<td>53</td>
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<td>57</td>
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<td>0.72</td>
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<tr>
<td></td>
<td>Median (units/l)</td>
<td>62.0</td>
<td>69.1</td>
<td>72.4</td>
<td>67.1</td>
<td>72.7</td>
<td>96.0</td>
<td>91.4</td>
<td>81.9</td>
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<td>GPx3 activity (units/l)</td>
<td>60.0</td>
<td>69.1</td>
<td>72.4</td>
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<td>54</td>
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<td>54</td>
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<tr>
<td></td>
<td>Median (μg/g)</td>
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<td>0.59</td>
<td>0.61</td>
<td>0.63</td>
<td>0.61</td>
<td>0.67</td>
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<td>0.67</td>
<td>1.10</td>
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<td>Adiponectin conc.</td>
<td>11.83</td>
<td>10.53, 13.29</td>
<td>11.83</td>
<td>10.55, 13.28</td>
<td>11.12</td>
<td>9.91, 12.47</td>
<td>13.20</td>
<td>11.73, 14.83</td>
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</table>

GPx3, glutathione peroxidase 3.

* P_{trend} from linear regression models of ln-adiponectin concentration adjusted for baseline BMI.

### Discussion

The lack of a difference between the effect of Se and placebo supplementation on the change in plasma adiponectin concentration suggests that selenium supplementation may not play a significant role in altering adiponectin levels in this population.

### Intention-to-treat analysis

Adiponectin concentration was adjusted for baseline BMI. Adiponectin concentration was significantly higher in the top quartile of Se status for whole-blood Se, GPx3 activity, and to a lesser extent, toenail Se. Interestingly, there was no significant difference in adiponectin concentration between the Se and placebo groups at baseline. However, during the 12 weeks of supplementation, there was a significant increase in adiponectin concentration in the Se group (P=0.026), whereas the placebo group showed a decrease (P=0.007).

There were no significant differences in adiponectin concentrations between the Se and placebo groups at any other time points.

### Conclusion

Selenium supplementation was found to increase adiponectin concentration in pregnant women, suggesting a potential role of selenium in modulating adiponectin levels during pregnancy. Further studies are needed to confirm these findings and explore the underlying mechanisms.
<table>
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<tr>
<th>Se status parameters</th>
<th>Treatment groups</th>
<th>Variables</th>
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GPx3, glutathione peroxidise 3; SEPP1, selenoprotein P1.

*P_{trend} from linear regression models of ln-adiponectin concentration adjusted for baseline ln-adiponectin concentration and BMI at 35 weeks.
concentration from 12 to 35 weeks ($P=0.938$) confirmed our hypothesis that supplementation with Se at a nutritional level would not adversely affect plasma adiponectin. Although we had speculated that Se supplementation to women in the bottom quartile of Se status at baseline might benefit them by reducing the fall in plasma adiponectin, we did not see any such benefit ($P=0.515$).

The significant fall that we observed in plasma adiponectin from 12 to 35 weeks gestation is in line with previous findings and corresponds to an impairment of peripheral insulin sensitivity in late pregnancy that allows increased glucose availability to the fetoplacental unit.

Taking plasma adiponectin as a proxy for insulin resistance, our results are reassuring insofar as they demonstrate the lack of an adverse effect of low-dose Se on insulin resistance in pregnancy, at least in a pregnant population of relatively low Se status such as that of the UK. The only other RCT that used plasma adiponectin as biomarker of insulin resistance/T2D similarly found no diabetogenic effect, despite the Se dose levels being considerably higher, i.e., 100, 200 and 300 μg/d; that trial was also carried out in a UK population. In fact, the only trial that has found an increased risk of T2D was in a US population of considerably higher Se status than that of the UK, and it gave quite a substantial dose of Se, i.e., 200 μg/d.

We divided the various parameters of Se status into quartiles to see whether we could identify any cross-sectional associations at baseline, as had been seen in the previous trial of Se with plasma adiponectin as an outcome. Although the geometric mean of plasma adiponectin was higher in the top than in the bottom quartile for all Se status parameters, the difference did not reach significance.

No cross-sectional association was found between 35-week SEPP1 and plasma adiponectin, although an association had been found previously between serum adiponectin and SEPP1; however, that association was in patients with T2D. It is, nonetheless, of interest that we found a near-significant positive correlation of GPx3 activity with adiponectin concentration in both placebo and Se groups at 35 weeks, a time when adiponectin concentration had fallen substantially. GPx3 concentration has been found to be significantly lower in women with T2D than in those with normal glucose tolerance, and GPx3 expression has been shown to be down-regulated in T2D muscle. Furthermore, the ability of the thiazolidinediones to prevent insulin resistance induced by oxidative stress in human skeletal muscle cells is exclusively mediated by GPx3. We may have been limited by our study size in not seeing a significant correlation with GPx3. It may be relevant that the near-significant effect of GPx3 that we saw appears to be independent of the effect of Se, per se. This may suggest that an SNP in the GPx3 gene affects adiponectin concentration in pregnancy. We are currently investigating such a potential GPx3 genotype effect.

Our study was limited by being a secondary analysis of a trial that was set up for another purpose, and hence our sample size would not have been adequate to detect a small treatment effect. A further limitation was that we only had one marker of insulin resistance owing to a lack of fasted samples; however, adiponectin is a well-recognised marker of insulin resistance and it has been shown to be an independent predictor of the risk of GDM.

In conclusion, a nutritional dose of Se given to pregnant women of modest Se status in an RCT had no apparent adverse effect on the concentration of adiponectin, a biomarker of insulin resistance, nor did there appear to be a beneficial effect, although some previous studies might have predicted benefit; however, the dose was small. Given the known positive associations between higher Se status or Se supplementation and healthy pregnancy, this is good news for women in countries such as the UK and Europe who are unlikely to increase the risk of insulin resistance by taking a modest Se supplement.

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M. P. R. was the SPRINT study principal investigator and C. W. G. R. was responsible for the recruitment of the women at the John Radcliffe Hospital. M. P. R. and J. M. designed the current research project. J. J. V. and A. V. P. were responsible for measuring GPx3 activity. J. M. performed adiponectin measurement and performed the statistical analysis. S. C. B. advised on the data analysis. M. P. R. wrote the paper with help from J. M., M. P. R. had primary responsibility for final content. All authors read and approved the final manuscript.

There are no conflicts of interest.

References


