Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition
Nutrition & Food Security Research Center

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2023; 8(1): 122-129 Website: jnfs.ssu.ac.ir

Effects of Selenium Supplementation on Incidence and Severity of Preeclampsia: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial

Fatemeh Mohsenpour; MD [1], Nahid Radnia; MD [*1,2], Maryam Ahmadi; MD [1], Ziba Mohsenpour; MD [3], Maryam Jamali; MD [1] & Mohammad Ali Mohsenpour; PhD [4,5]

[1] Department of Obstetrics and Gynecology, Fatemieh Hospital, Hamadan University of Medical Sciences and Health Services, Hamadan, Iran; [2] Clinical Research Development Unit, Fatemieh Hospital, Hamadan University of Medical Sciences and Health Services, Hamadan, Iran; [3] Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [4] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran; [5] Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.

ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 8 Feb 2022
Revised:6 Apr 2022
Accepted: 15 May 2022

Corresponding author:
nahid.radnia.2020@gmail.com
Fatemieh Hospital, Fatemieh Hospital, Pasdaran St, Hamadan, Iran.

Postal code: 6517789971
Tel: +98 81 38255890

ABSTRACT

Background: Preeclampsia is a serious hypertensive condition of pregnancy associated with high maternal and fetal morbidity and mortality. In this study, the effect of selenium supplementation on the incidence and severity of preeclampsia in pregnant women was evaluated. **Methods:** The present double-blind, placebo-controlled, parallel study was registered at Fatemieh Hospital of Hamadan, Iran. One hundred eighty women in the first trimesters of pregnancy were assigned to either selenium (SG, n = 90) or placebo (PG, n = 90) groups. SG and PG received 100 µg of selenium supplement or placebo per day, respectively. **Results:** In this study, no significant difference was observed between two groups in terms of age, body mass index, and serum selenium before the intervention ($P > 0.05$). The incidence of preeclampsia in the SG and PG was 9 and 5, respectively ($P = 0.28$). There was no statistically significant difference between sex and Apgar score of neonates in the two groups ($P = 0.73$). The mean birth weight, systolic and diastolic blood pressure in the SG was significantly higher than PG ($P = 0.003$, 0.01, and 0.007, respectively). The mean gestational age in the SG was insignificantly lower than the PG ($P = 0.41$). After the study, preeclampsia incidence was not significant between the groups ($P = 0.28$). **Conclusion:** The administration of 100 µg of selenium supplementation in pregnant women, had no effect on decreasing preeclampsia, but it may reduce the severity of preeclampsia.

Keywords: *Selenium; Supplement; Preeclampsia; Pregnancy; RCT*

Introduction

Preeclampsia is a condition where systolic blood pressure amount is more than 140 mm Hg and diastolic blood pressure is ≥ 90 mm Hg, when measured at least twice with an interval of at least 4-6 hours after 20th weeks of gestation along with proteinuria (resulted in 300 mg/24 h

This paper should be cited as: Mohsenpour F, Radnia M, Ahmadi M, Mohsenpour Z, Jamali M, Mohsenpour MA. ***Effects of Selenium Supplementation on Incidence and Severity of Preeclampsia: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial.*** *Journal of Nutrition and Food Security (JNFS)*, 2023; 8 (1): 122-129.

or more than +1 dipstick) (Cunningham *et al.*, 2014).

High blood pressure disorders during pregnancy, including preeclampsia involve a wide range of conditions that may have a substantial impact on maternal morbidity and mortality, and also fetal and neonatal mortality. Its incidence rate is estimated to be 3-10% of pregnancies (Duley, 2009, Wallis *et al.*, 2008). Preeclampsia and its related conditions are one of the most causes of maternal mortality in the world (Duley, 2009). Although the rate of preeclampsia-related mortalities is low in developed countries, the rate of related morbidities is high and is one of the important causes of maternal hospitalization in ICU (Duley, 2009, Porreco and Barkey, 2010). It is estimated that about 12-25% of intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) cases, as well as 15-20% of preterm births are because of preeclampsia with outcomes, including increased severe diseases and neonatal mortality (Duley, 2009, Goldenberg, 1998).

In has been suggested that in preeclamptic women, plasma selenium levels (Maleki *et al.*, 2011, Mistry *et al.*, 2008) and selenium levels in toe nails (Rayman *et al.*, 2003) decreased significantly. This is also accompanied by reduced endogenous antioxidant activity (Mistry *et al.*, 2008, Vanderlelie and Perkins, 2011) and increased oxidative stress activity (Hubel, 1999, Perkins, 2006, Vanderlelie and Perkins, 2011, Wang and Walsh, 1998). Various hypotheses have been put forward, such as increased or abnormal immune response, genetic predisposition, endothelial cell damage, increased free radicals, changes in nitric oxide level, and trace elements shortage. Among different factors, numerous diagnostic tests have been suggested for early prediction and screening of preeclampsia (Cunningham *et al.*, 2014, Gibbs *et al.*, 2008).

Among these hypotheses, the trace elements shortage hypothesis has gained prominence attention recently. The reduced level of serum selenium and its relation to the incidence of preeclampsia in comparison with normal pregnant women have been reported in the literature (Atamer *et al.*, 2005, Ilhan *et al.*, 2002, Mahomed *et al.*, 2000, Orhan *et al.*, 2003, Rayman, 2012). Accordingly, a group of researchers suggest the measurement of serum concentration of selenium for early screening of preeclampsia (Mistry *et al.*, 2008, Rayman, 2012). Thus, purpose of this double-blind, controlled clinical trial was to assess the effect of selenium supplementation treatment on preeclampsia in pregnant women referring to Fatemieh Hospital of Hamadan, Iran.

Materials and Methods

Study design and participants: In the present double-blinded randomized controlled clinical trial, 180 primigravida first-trimester pregnant women who referred to Fatemieh Hospital of Hamadan. The inclusion criteria were singleton pregnancy, first trimester, no history of chronic hypertension, and not using any selenium supplement during the last year. The exclusion criteria included using any medication except ferrous sulfate and folic acid supplements, suffering from any disease, such as diabetes, infections, and thyroid, and following special selenium rich diet (according to dietitian). Sample size was calculated based on previous studies with considering a 20% attrition rate in order to achieve the necessary sample size to have power of 80% and significance level of 0.05 (Tara *et al.*, 2010).

After signing a written informed consent form by participants, age, height, and weight were recorded. Block randomization was used to assign the participants into selenium (SG) and placebo (PG) groups. In order to blind personnel and participants, the participants and the medical staff, including the physician who measured blood pressure were unaware of the assigned group. The SG received 100 μg of selenium supplement per day (half a 200 mg tablet) until the end of pregnancy. The PG received a placebo tablet similar in size and shape, for blinding the

[DOR: 20.1001.1.24767417.2023.8.1.15.1]
[DOI: 10.18502/jnfs.v8i1.11777]

personnel and participants, with the selenium tablet.

Measurements: For determination of serum selenium, A 5 ml blood sample were taken. Subsequently, using the electrothermal atomic absorption spectrometry with Zeeman background correction with a palladium chloride chemical modifier, serum selenium concentrations were assessed (coefficient of variation was 3.7%).

Systolic and diastolic blood pressures were measured before the intervention and routinely during visits based on the national instruction. Blood pressure was measured using a standard mercury manometer, in sitting and lying positions. Measured blood pressure ≥ 140 / 90 (mmHg) was retested with an interval of at least 6 hours in order to be considered as a hypertensive mother.

Pregnancy and delivery outcomes in both groups, including gestational age, birth weight, and first minute Apgar score were measured and recorded in a checklist.

Preeclampsia definition: Mother was categorized as mild preeclampsia with blood pressure of 140 / 90 (mmHg) to 160 / 110 (mmHg) and severe preeclampsia with blood pressure of higher than 160 / 110 (mmHg) without response to IV Labetalol or IV hydralazine treatment or with severe preeclampsia clinical signs and symptoms.

Ethical considerations: All participants signed the written informed consent form. The study protocol was approved by the Research Committee of Hamadan University of Medical Sciences, Hamedan, Iran, and registered at the Iranian Registry of Clinical Trials (IRCT201702109014N143).

Data analysis: The data were analyzed using SPSS software version 16. Mean ± standard deviation (SD) was used to report the quantitative data and the qualitative data were reported using frequency. Chi-square test was performed in order to compare the frequency of the incidence of preeclampsia between both groups, and independent *t-test* was done for between-group analysis of age and body mass index (BMI). A nonparametric Mann-Whitney *test* was used to compare the difference of systolic and diastolic blood pressure, gestational age, birth weight, and first minute Apgar score between groups. A P-value of less than 0.05 was considered significant.

Results

Figure 1 shows the procedure of the study. The mean of serum selenium level before the intervention for women with and without preeclampsia were 95.61 ± 30.16 and 87.00 ± 14.99 μg/ml, respectively that were not significantly different ($P = 0.07$). **Table 1** shows the baseline data. As shows, the SG and PG were not significantly different in terms of baseline characteristics, including age, BMI, serum selenium level, and systolic or diastolic blood pressure ($P > 0.05$).

Table 2 indicates that, frequency of preeclampsia was 9 and 5 in the SG and PG, respectively, but the difference was not significant ($P = 0.28$). Regarding the percentage of preeclampsia, 8 (88.9%) out of 9 in the SG had mild and 1 (11.1%) had severe preeclampsia. However, in the PG, 1 (20%) out of five had mild and 4 (80%) had severe preeclampsia. The analysis showed that the severity of preeclampsia in the SG was significantly lower than PG ($P = 0.02$). Analyzing the incident of severe preeclampsia among all the participants of groups, no significant different was seen ($P = 0.17$).

Table 3 indicates that, after the study, participants in the SG had a significantly higher systolic blood pressure than the PG (100.22 ± 12.19 and 97.39 ± 12.29 mmHg, respectively) ($P = 0.01$). The same trend was seen for diastolic blood pressure ($P = 0.007$), but the mean changes between group was not significant for systolic ($P = 0.87$) or diastolic ($P = 0.73$) blood pressure. Participants who were in the SG give birth to children with higher birth weight ($P = 0.003$), but pregnancy duration for both groups was not statistically different (38.95 ± 1.65

[DOR: 20.1001.1.24767417.2023.8.1.15.1]
[DOI: 10.18502/jnfs.v8i1.11777]

weeks for the SG vs. 39.15 ± 1.66 week for the PG, *P* = 0.41). Both groups gave birth to the same number of girls (n = 41) and boys (n = 49). The Apgar score was not different between the groups (*P* = 0.73).

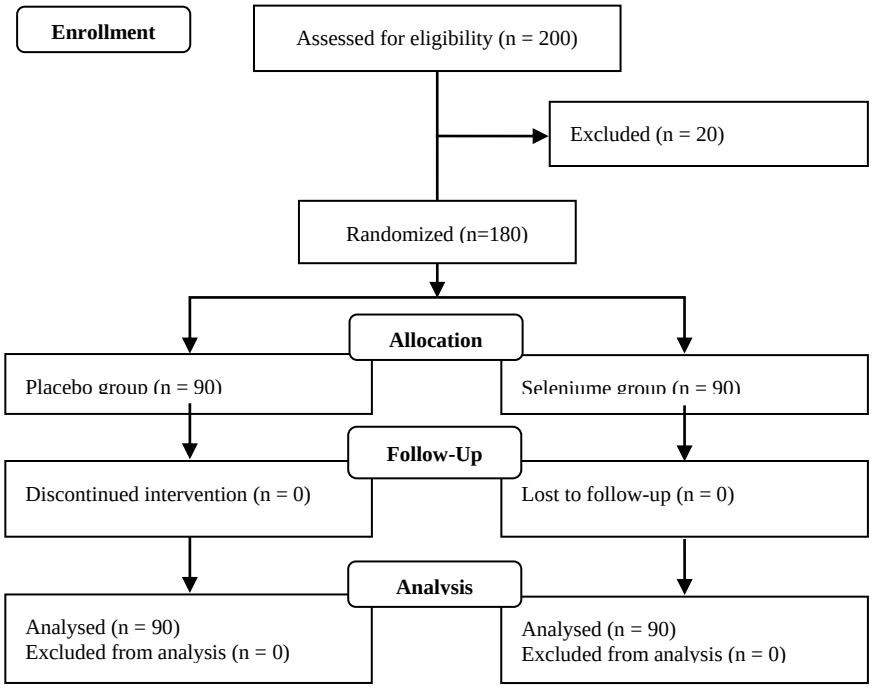

Figure 1. CONSORT flow diagram demonstrating the study procedure.

Table 1. Mean (±SD) of baseline characteristics of the participants of the selenium and placebo groups.

Variables	Selenium group (n = 90)	Placebo group (n = 90)	P-value[a]
Maternal age (year)	27.54 ± 6.02	28.77 ± 5.36	0.06
Body mass index (kg/m^2)	24.17 ± 2.79	23.99 ± 3.10	0.40
Serum selenium (µg/l)[b]	95.69 ± 31.11	93.52 ± 27.54	0.62
Systolic blood pressure (mmHg)	99.20 ± 10.18	97.30 ± 11.46	0.24
Diastolic blood pressure (mmHg)	67.30 ± 7.09	62.89 ± 8.24	< 0.001

[a]: Independent two sample t-test, [b]: Normal value: 116 – 146 (µg/l)

Table 2. Frequency distribution of preeclampsia for the selenium and placebo groups.

Variables	Selenium group (n = 90)		Placebo group (n = 90)		P-value
	N	%	N	%	
No Preeclampsia	81	90.0	83	94.3	0.28[a]
Preeclampsia	9	10.0	5	5.7	
Mild	8	88.9	1	20.0	0.02[b]
Severe	1	11.1	4	80.0	

[a]: Chi-square test, [b]: Fisher's exact test.

Table 3. Comparison of the outcomes variables in the selenium and placebo groups.

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[DOI: 10.18502/jnfs.v8i1.11777]

Variables	Selenium group (n = 90)	Placebo group (n = 90)	P-value
Serum selenium level (µg/l)			
Before	95.69 ± 31.11[d]	93.52 ± 27.54	0.62[a]
After	102.31 ± 28.12	98.60 ± 29.33	0.38[a]
Mean differences	6.62 ± 41.93	5.08 ± 40.23	0.80[b]
P-value[c]	0.13[c]	0.23[c]	
Systolic blood pressure (mmHg)			
Before	99.20 ± 10.18	97.30 ± 11.46	0.24[a]
After	100.22 ± 12.19	97.94 ± 12.29	0.01[b]
Mean differences	1.02 ± 15.88	0.64 ± 16.80	0.87[b]
P-value	0.54	0.71	
Diastolic blood pressure (mmHg)	67.30 ± 7.09	62.89 ± 8.24	<0.001[a]
Before	68.12 ± 8.06	63.16 ± 7.28	0.007[b]
After	0.82 ± 10.73	0.27 ± 10.99	0.73[b]
Mean differences	0.82 ± 10.73	0.27 ± 10.99	0.73[b]
P-value	0.46[c]	0.81[d]	
Neonatal weight (g)	3282.22 ± 356.82	3123.33 ± 365.06	0.003[b]
Gestational age (week)	38.95 ± 1.65	39.15 ± 1.66	0.41[a]
First minute Apgar score	9.47 ± 0.74	9.36 ± 1.27	0.73[b]
Neonate gender			1[e]
Boy	49 (54.4)[f]	49 (54.4)	
Girl	41 (45.6)	41 (45.6)	

[a]: Independent *t-test*, [b]: Mann-Whitney U *test*, [c]: Paired *t-test*, [d]: Mean ± SD, [e]: Chi square *test*, [f]: N (%).

Discussion

In the present study, selenium supplementation did not reduce the incidence of preeclampsia, but it affected the severity. Preeclampsia and increased blood pressure during pregnancy have a significant impact on maternal health and increase the risk of maternal, fetal, and neonatal mortality (Duley, 2009, Wallis *et al.*, 2008).

Previous studies have shown that there is a significant direct correlation between maternal and neonatal serum selenium level and there is a relationship between low maternal serum selenium level and preterm birth (Alipour *et al.*, 2014). Considering pieces of evidence (Barati *et al.*, 2014, Hubel, 1999, Maleki *et al.*, 2011, Mistry *et al.*, 2008, Özkaya *et al.*, 2011, Perkins, 2006, Rayman *et al.*, 2003, Vanderlelie and Perkins, 2011, Wang and Walsh, 1998), this clinical trial was conducted to investigate the effect of selenium supplementation on the risk of preeclampsia in pregnant women. The results showed no statistically significant difference in the incidence of preeclampsia between women receiving selenium supplements and the placebo.

In a study by Davaryari (Davaryari *et al.*, 2011), which compared the serum level of selenium in 35 preeclamptic pregnant women with 35 normal pregnant women, the mean serum concentration of selenium in the former was higher than in the latter, which is inconsistent with the present study. On the other hand, in a study conducted by Ghaemi (Ghaemi, 2013) on plasma selenium level and its relationship with preeclampsia and other pregnancy outcomes, 38 primigravida women with preeclampsia and 38 primigravida normal women were examined. Results showed that the serum level of selenium in the preeclampsia group was significantly lower than in the control group. However, no statistically significant difference was found between the two groups in terms of neonatal birth age, birth weight, and Apgar score. Contrary to these findings, the mean age of newborns of mothers who received selenium supplement was significantly higher than that of the PG in the present study, which is in line with the study by Ghaemi *et al.* (Ghaemi, 2013). However, no statistically significant difference was found between the SG and PG in neonatal birth age and Apgar score.

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[DOI: 10.18502/jnfs.v8i1.11777]

Rayman *et al.* (Rayman *et al.*, 2003) compared 53 preeclamptic and 53 normal pregnant women in terms of serum level of selenium. They showed that the serum level of selenium in preeclamptic women was significantly lower than normal women. In the present study, the pre-intervention mean serum level of selenium in preeclamptic women was lower than in normal women. Ghaemi and Rayman (Ghaemi, 2013, Rayman *et al.*, 2003) reported that the difference between the two groups was not statistically significant before the study. This might be attributed to the small number of preeclamptic pregnant women in the present study compared to other studies (14 compared to 38 and 53 women, respectively).

In a clinical trial carried out on the impact of selenium supplementation of the incidence of preeclampsia, Tara *et al.* (Tara *et al.*, 2010) examined 166 pregnant women divided into two groups. The intervention group received 100 µg of selenium daily until the end of pregnancy and the control group received a placebo. No case of preeclampsia was reported in the intervention group, while three cases were found in the control group. However, this difference was not statistically significant between the groups, which is in line with the present study. There was also a significant increase after the intervention in the mean systolic and diastolic blood pressure, and in the levels of high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), and CRP in both groups. In the study by Tara *et al.* (Tara *et al.*, 2010), contrary to the current study, no preeclampsia was occurred in the intervention group. This could be due to higher selenium level in the participants of their study. In their study (Tara *et al.*, 2010) selenium level increased in the intervention group significantly but not in control group. The present study aims to perform supplementation in order to correct serum selenium level. Thus, the supplement dosage was not changed in the present study protocol.

In an ecological study, Vanderlelie *et al.* (Vanderlelie and Perkins, 2011) examined the incidence and prevalence of preeclampsia and the serum level of selenium in different parts of the world. Comparing the data on the incidence rate of preeclampsia and the serum level of selenium showed that the incidence rate of preeclampsia is significantly low in regions where the plasma level of selenium is high. Since ecological studies are not highly valid in terms of proving causal relations and may include numerous confounders, the findings of Vanderlelie *et al.* (Vanderlelie and Perkins, 2011) cannot imply that there is a relationship between the plasma level of selenium and the incidence rate of preeclampsia.

In order to identify the relation between selenium and preeclampsia, Da Silva *et al.* (da Silva *et al.*, 2017) compared 32 normotensives, 20 chronic hypertensive, and 38 preeclamptic pregnant women in terms of serum selenium levels and performed postpartum follow-up. No significant difference was observed among the three groups in mean serum selenium levels and no significant relationship was found between serum selenium level and other pregnancy outcomes. In the present study, no statistically significant difference was found in the incidence of preeclampsia between the SG and PG, but it was effective in reducing the severity of preeclampsia. There was also a significant difference in serum selenium levels of pregnancy onset between preeclamptic and non-preeclamptic women.

One of the limitations this study was the small number of qualified patients and non-adherence to treatments by some of the participants. A 20% attrition rate was set in order to achieve the necessary sample size. Moreover, financial limitations did not allow post-intervention measurement of the serum levels of selenium in the long term. It seems that biological research in this field and multi-centered studies with bigger sample size or pre-pregnancy prescription of selenium can better reveal the effects of selenium element on preeclampsia and other pregnancy outcomes.

Conclusion

Selenium is a trace element for human health and in addition to its antioxidant effects plays important roles in vital body mechanisms and activities. A preventive effects of selenium on the

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incidence of preeclampsia was not confirmed statistically in this study. More well designed future studies are recommended in order to make a better conclusion for this case.

Acknowledgement

This paper is part of a specialty doctoral dissertation in gynecology approved in Hamadan University of Medical Sciences, Hamadan, Iran. Thanks are owed to the deputy for research and technology at Hamadan University of Medical Sciences, managers and the staff of Fatemieh Hospital, and all the people who helped to carry out this research. This study was financially supported by the Hamadan University of Medical Sciences and Health Services.

Authors' contributions

Mohsenpour F, Radnia N, and Ahmadi M designed research; Mohsenpour F, Mohsenpour Z, and Jamali M conducted research; Ahmadi M, Jamali M, and Mohsenpour MA analyzed data; and Mohsenpour F, Mohsenpour Z, and Mohsenpour M wrote the manuscript. Radnia N had primary responsibility for final content. All authors read and approved the final manuscript

Conflict of interest

Authors have no conflict of interest to declare. No external grant was used to provide the selenium supplements or the placebo.

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[DOI: 10.18502/jnfs.v8i1.11777]