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Research Article

# Maternal and Neonatal Selenium Levels in Preeclampsia and Its Relation with Disease Severity and Neonatal Outcomes

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## Abstract

**The purpose of this study** was to assay the serum selenium levels in preeclampsia without severe features and in pre-eclamptic with severe features cases and its relation to the neonatal birth weight.

**Subjects and methods**: In this study, **160** participants were divided into the 3 groups: *group 1:* consisted of 60 patients with severe preeclampsia*, group 2:* consisted of 60 patients of non-severe preeclampsia (without severe features), and *group 3:* consisted of 40 normal pregnant women.

After delivery the cases with severe preeclampsia and the cases with non-severe preeclampsia were subdivided into two subgroups: a subgroup with low birth weight neonates, and a subgroup with average birth weight neonates.

Serum selenium levels (µg/L) were determined by using spectrophotometric method using azure B as a chromogenic reagent.

**Results**: Maternal mean serum selenium levels were statistically significantly decreased among cases with preeclampsia as compared to normal pregnant controls ($p< 0.0001$), and among the cases with severe preeclampsia compared to the non-severe preeclampsia cases ($p< 0.0001$). Also, low maternal and cord serum selenium levels were significantly decreased in low birth weight neonates as compared with normal birth weight neonates in cases with preeclampsia.

**Conclusion:** Maternal serum selenium levels were significantly decreased in cases with preeclampsia. Selenium supplementation may be suggested to prevent preeclampsia. Studies are needed on large number of pregnant women to determine possible importance of dietary selenium supplementation as regard the prevalence of preeclampsia.

**Key words:** Selenium, Preeclampsia, Low birth weight, Normal birth weight.

## Introduction

Preeclampsia (PET) is a pregnancy-specific multi-systemic disease and most often occurs in primigravidae [1]. It has now been well established that mothers with preeclampsia are at increased risk of cardiovascular disease later in life [2, 3].

Preeclampsia is a complex syndrome of unknown cause. It may be due to immunological factors, increased vascular sensitivity to pressor hormones and prostaglandins, or due to oxidation stress. Endothelial cell dysfunction caused by increased reactive oxygen species results in generalized vasoconstriction, causing reduction of blood supply to many organs [4]. Also, shallow trophoblastic invasion of the spiral arteries results in diminished placental perfusion and the generation of significantly increased levels of reactive oxygen species (ROS) within the preeclamptic placenta [5].

Selenium is essential for the proper function of the seleno-enzyme that acts as antioxidant involved in the defense mechanism against the adverse effects of reactive oxygen species (ROS) to avoid damage of the endothelial cells [6]. Also, there have been reports of decreased selenoprotein production in preeclamptic pregnancy including important endogenous antioxidants, such as glutathione peroxidase and thioredoxin reductase *[6]*.

## Aim of The Work

The purpose of this work was to measure the serum selenium levels as an oxidative stress trace element in preeclampsia.

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## Material and Methods

This study was conducted at the Obstetrics & Gynecology department, Mansoura University Hospital, Mansoura University, Egypt. Informed written consent was taken from each patient prior to any procedure.

In this study, **160** participants were recruited from the obstetric department of Mansoura University Hospital, Mansoura, Egypt, during the period between December 2015 and October 2018, in accordance with the following inclusion/exclusion criteria.

### Participants

In this work **160** participants **were studied including *the following groups:***

**Group 1:** consisted of 60 cases of non-severe preeclampsia (cases without severe features).

**Group 2:** consisted of 60 cases of severe preeclampsia (cases with severe features).

**Group 3:** consisted of 40 normal pregnant women as control cases.

**The cases with preeclampsia** were subdivided **after delivery** into a subgroup with low birth weight neonates (birth weight were below the 10$^{th}$ percentile**, and** a subgroup with average birth weights neonates (more than the 10$^{th}$ percentile, according to the chart of ***Alexander et al*** [7].

***Subgroup 1A:*** consisted of 21 cases with non-severe preeclampsia (without severe features) giving birth to low birth weight neonates.

***Subgroup 1B:*** consisted of 39 cases with non-severe preeclampsia (without severe features) giving birth to normal birth weight neonates.

***Subgroup 2A:*** consisted of 26 cases with severe preeclampsia giving birth to low birth weight neonates.

***Subgroup 2B:*** consisted of 34 cases with severe preeclampsia giving birth to normal birth weight neonates.

**Inclusion criteria:** The cases included in this study had no history of hypertension before pregnancy and had documented normal blood pressure in the first trimester.

Preeclampsia (PET) is defined as de novo hypertension (>140/90 mm Hg) and proteinuria (> 0.3 g per 24 hours) during the second half of pregnancy [8].

According to ACOG Task Force on Hypertension [8], the term mild preeclampsia (PET) is replaced by non-severe preeclampsia (preeclampsia without severe features). ***Severe preeclampsia (PET with severe features)*** is considered if systolic or diastolic blood pressures values ≥160 or 110 mm Hg, respectively, occurring twice, 4 hours apart at bed rest [8].

These patients were subjected to the following: full history, general and abdominal examination. The mothers underwent medical interviews on admission to determine their age, full medical history, patients' habits as smoking, and body mass index. Gestational age was determined by last menstrual period and ultrasonic scanning. Neonatal birth weights at delivery were measured.

**Exclusion criteria** are cases above 35 years, smoking, pregnant cases with chronic hypertension, heart disease, thyroid disorders, diabetes mellitus, and multi-fetal gestation.

### Ethical approval

The study was approved by the IRB committee of Faculty of Medicine, Mansoura University, Egypt [code number: R/15.10.13, date: 12/12/2015]. Informed written consents were taken from the cases.

### Sampling

In the normal pregnant cases, in cases with without severe features preeclampsia & cases with preeclampsia with severe features attending for delivery, three ml of maternal venous blood were obtained before delivery, and umbilical cord blood samples (3 ml) were obtained just after delivery of the fetus.

All samples were collected in a vaccutainer tube with gel and the collected blood samples were centrifuged at 3000 *g* for 15 min. The serum was separated, and kept in a clean tube at -20 °C till the time of assay.

### Methods of selenium assay

Selenium levels (µg/L) in the serum were assayed by *spectrophotometric method using azure B as a chromogenic reagent* [9]. The method is based on the reaction of selenium with potassium iodide in acidic medium to liberate iodine. The liberated iodine bleaches the violet color of azure B. The absorbance was measured at 644 nm against distilled water as a reagent blank. The absorbance corresponding to the bleached color, which in turn corresponds to the selenium concentration, was obtained by subtracting the absorbance of blank solution from that of the test solution.

The amount of the selenium was computed from the calibration graph.

### Statistical Analysis

Statistical analyses were performed by using the Statistical Package for Social scientists (SPSS) computer database for windows 7 (SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used to describe data. In the analysis, un-paired t-test was used to test for significant change in quantitative data. *P* value was considered significant if less than 0.05.

## Results

Table 1 represents the clinical details and the serum selenium levels in all cases with severe preeclampsia (PET), all cases with non-severe PET, and control group cases with normal pregnancy.

The values of Systolic blood Pressure (SBP) & Diastolic Blood Pressure (DBP) were significantly increased ($p$<0.0001) in severe PET and in non-severe PET as compared with the control values. On the other hands, gestational age, neonatal birth weight, maternal selenium and umbilical cord blood selenium were significantly decreased ($p$<0.0001) in severe PET and in non-severe PET as compared with the control values.

The neonatal birth weight in cases with severe PET was significantly decreased as compared with the neonatal birth weight in cases with non-severe PET ($p$=0.033). The maternal and cord blood selenium levels were significantly lower in severe PET as compared with the non-severe PET ($p$<0.0001)

**Table 1:** Clinical details and selenium levels *(µg/L)* in the studied groups.

| | | All non-severe PET (60 cases) | All SeverePET (60 cases) | Normal pregnancy *(40 cases)* | P Value | | |
|---|---|---|---|---|---|---|---|
| | | | | | P1 | P2 | P3 |
| Age (Years) | Mean | **27.133** | **27.08** | **27.525** | =0.251* | =0.092* | =0.999* |
| | ±SD | **± 1.78** | **± 1.123** | **± 1.467** | | | |
| Systolic BP | Mean | 148.383 | 162.15 | 122.925 | <0.0001 | <0.0001 | <0.0001 |
| (mmHg) | ±SD | ± 3.801 | ± 2.357 | ± 7.930 | | | |
| Diastolic BP *(mmHg)* | Mean | 91.733 | 92.033 | 72.525 | <0.0001 | <0.0001 | =0.217* |
| | ±SD | ± 1.561 | ± 2.577 | ± 2.099 | | | |
| Gestational Age *(Ws)* | Mean | 36.78 | 36.33 | 39.925 | <0.0001 | <0.0001 | 0.081* |
| | ± SD | ± 1.514 | ± 1.244 | ± 0572 | | | |
| Birth weight *(gm)* | Mean | 3001.5 | 2842.83 | 33498.75 | <0.0001 | <0.0001 | =0.033 |
| | ± SD | ± 385.807 | ± 420.008 | ± 108.892 | | | |
| *Maternal selenium* (µg/L) | Mean | 55.617 | 39.933 | 69.925 | <0.0001 | <0.0001 | <0.0001 |
| | ± SD | ± 15.899 | ± 9.855 | ± 7.896 | | | |
| *Cord selenium* (µg/L) | Mean | 45.9 | 35.2 | 71.95 | <0.0001 | <0.0001 | <0.0001 |
| | ± SD | ± 12.071 | ± 10.381 | ± 18.312 | | | |

PET: preeclampsia
*p value >0.05 is not significant.
- *p*1: P value on comparing control *(*group3) *versus* all non-severe PET.
- *p*2: P value on comparing control *(*group 3) versus all severe PET.
- *p*3: P value on comparing all non-severe PET versus all severe PET.

**Table 2:** Clinical details and selenium levels *(µg/L)* in the studied cases giving birth to *normal birth weight neonates*.

| | | Non-severe Subgr. 1B (39 cases) | Severe PET Subgr. 2B (34 cases) | Group 3 *control* (40 cases) | P value | | |
|---|---|---|---|---|---|---|---|
| | | | | | P1 | P2 | P3 |
| Age (Years) | Mean | 26.974 | 27.525 | 27.525 | =0.151 | =0.369 | =0.151 |
| | ±SD | ± 1.885 | ± 1,467 | ±1.467 | | | |
| Systolic BP | Mean | 149 | 162.471 | 122.925 | <0.0001 | <0.0001 | <0.0001 |
| (mmHg) | ±SD | ± 4.098 | ±2.529 | ±7.930 | | | |
| Diastolic BP *(mmHg)* | Mean | 91.59 | 92.529 | 72.525 | <0.0001 | <0.0001 | =0.085 |
| | ±SD | ± 1.446 | ± 2.977 | ± 2.099 | | | |
| Gestational Age *(Ws)* | Mean | 37.667 | 37.765 | 39.925 | <0.0001 | <0.0001 | =0.685 |
| | ±SD | ± 1.009 | ± 1.046 | ± 0572 | | | |
| Birth weight *(gm)* | Mean | 3264.103 | 3182.35 | 33498.75 | =0.0084 | <0.0001 | =0.053 |
| | SD | ± 164.216 | ± 191.043 | ± 108.892 | | | |
| Maternal selenium | Mean | 59.846 | 41.059 | 69.925 | =0.0006 | <0.0001 | <0.0001 |
| | ± SD | ± 14.762 | ± 8.944 | ± 7.896 | | | |
| Cord selenium | Mean | 49.692 | 38.794 | 71.95 | <0.0001 | <0.0001 | <0.0001 |
| | SD | ± 10.441 | ± 9.038 | ± 18.312 | | | |

PET: preeclampsia. *p value >0.05 is not significant. Subgr.: subgroup.
*p*1: P value on comparing group 3 (control) *versus* subgroup 1 B (non-severe PET).
*p*2: P value on comparing group 3 (control) *versus* subgroup 2 B (severe PET).
*p*3: P value on comparing subgroup 2 B (severe PET) *versus* subgroup 1B (non-severe PET).

Table 2 shows the clinical details and serum selenium levels in the studied cases giving birth to normal birth weight neonates (subgroup 1B & subgroup 2B)..

The cases with non severe PET (subgroup 1B) and the cases of severe PET (subgroup 2B) giving birth to normal birth weight had a statistically significant decreased maternal serum selenium levels as compared to the levels of normal pregnant women ($p$<0.0001, $p$= 0.0006, respectively), while the cord blood selenium levels were significantly decreased in both PET groups ($p$<0.0001) as compared with normal pregnant women levels.

The maternal serum selenium levels and the cord blood serum selenium in subgroup 2 B cases with severe PET showed a highly significant decrease levels as compared with subgroup 1 B cases with non-severe PET ($p$< 0.0001).

Table 3 represents the clinical details and selenium levels in the studied cases giving birth to low-birth weight neonates (subgroup 1A and subgroup 2A) as compared with the control cases with normal pregnancy (group 3).

The cases with non severe PET (subgroup 1A) and the cases of severe PET (subgroup 2A) giving birth to low birth weight had a statistically significant decreased values of all parameters except age, as compared with the normal pregnant control cases ($p$<0.0001).

Subgroup 2A cases had significantly lower values of neonatal birth weight ($p$<0.0001), maternal serum selenium levels (p=0.019) and cord blood selenium levels ($p$=0.0134) as compared with subgroup 1A cases.

**Table 3:** Clinical details and *maternal* selenium levels *(µg/L)* in cases with preeclampsia giving birth to *low-birth weight* neonates as compared with the neonates of the control cases with normal pregnancy.

| | | Subgroup 1A Non-severe PET (21 cases) | Subgroup 2A Severe PET (26 cases) | Group 3 control (40 cases) | P value | | |
|---|---|---|---|---|---|---|---|
| | | | | | p1 | p2 | p3 |
| Age (Years) | Mean | 27.429 | 27.0 | 27.525 | =0.813 | =0.123 | =0,276 |
| | ± SD | ± 1.568 | ± 1.0954 | ± 1.467 | | | |
| Systolic BP | Mean | 147.238 | 161.751 | 122.925 | <0.0001 | <0.0001 | <0.0001 |
| (mmHg) | ± SD | ± 2.238 | ± 7.930 | ± 7.930 | | | |
| Diastolic BP *(mmHg)* | Mean | 92.0 | ± 91.385 | 72.525 | <0.0001 | <0.0001 | = 0.244 |
| | ± SD | ± 1.761 | ± 1.791 | ± 2.099 | | | |
| Gestational Age *(Ws)* | Mean | 35.143 | ± 35.154 | 39.925 | <0.0001 | <0.0001 | = 0.965 |
| | ± SD | ± 0.854 | ± 0.834 | ± 0572 | | | |
| Birth weight *(gm)* | Mean | 2513.81 | 2398.85 | 33498.75 | <0.0001 | <0.0001 | <0.0001 |
| | ±SD | ± 60.455 | 79.767 | ± 108.892 | | | |
| Maternal selenium | Mean | 47.672 | 38.462 | 69.925 | <0.0001 | <0.0001 | =0.019 |
| | ± SD | ± 15.231 | 10.937 | ± 7.896 | | | |
| Cord selenium | Mean | 38.857 | 30.5 | 71.95 | <0.0001 | <0.0001 | = 0.0134 |
| | ± SD | ± 11.943 | 10.293 | ± 18.312 | | | |

PET: preeclampsia. *p value >0.05 is not significant.
*p*1: P value on comparing group 3 (control) *versus* subgroup 1 B (non-severe PET).
*p*2: P value on comparing group 3 (control) *versus* subgroup 2 B (severe PET).

**Table 4:** *Maternal* serum selenium levels (µg/L) before delivery comparing cases giving birth *to normal birth weight infants* to cases giving birth to *low birth weight infants.*

| | Non-severe PET | | Severe PET | | P value (subgroups in the same row) |
|---|---|---|---|---|---|
| | Subgroup | Mean ± SD (µg/L) | Subgroup | Mean ± SD (µg/L) | |
| Low Birth Weight | 1A (21 cases) | 47.672 ±15.231 | 2A (26 cases) | 38.462 ±10.937 | **=0.019** |
| Normal birth Weight | 1B (39 cases) | 59.846 ± 14.762 | 2 B (34 cases) | 41.059 ± 8.944 | **< 0.0001** |
| *P value* (subgroups in the same column). | | **<0.004** | | **= 0.316** | |

**Table 5:** Comparison of serum cord selenium levels *(µg/L)* between low birth weight and normal birth weight neonates.

| | Non-severe PET | | Severe PET | | P value (Subgroups in the same row) |
|---|---|---|---|---|---|
| | Subgroup | Mean ± SD (µg/L) | Subgroup | Mean ± SD (µg/L) | |
| Low Birth Weight | 1A (21 cases) | 38.857 ± 11.945 | 2 A *(26 cases)* | 30.5 ± 10.293 | = 0.0134 |
| Normal birth Weight | 1B (39 cases) | 49.692 ± 10.441 | 2 B (34 cases) | 38.794 ± 9.038 | <0.0001 |
| P *value* (Subgroups in the same column). | | = 0.0006 | | = 0.0016 | |

PET: preeclampsia
Subgr.: subgroup.

Table 4 represents the ***maternal serum selenium*** levels before delivery comparing cases giving birth *to normal birth weight infants* (NW) and *low birth weight infants (LBW).*

In cases with non-severe PET the maternal serum selenium concentrations were significantly lower in subgroup 1A cases as compared with subgroup 1B cases (*p*= 0.004). In subgroup 2A cases with severe PET, the maternal serum selenium levels were not significantly lower as compared with subgroup 2 B (*p*= 0.316).

The subgroups 2A and 2 B cases of severe PET had a significantly decreased maternal selenium levels as compared with subgroups 1A and 1B cases of non-severe PET (*p* =0.019 & p<0.0001, respectively).

Table 5 represents comparison between the serum cord selenium levels in preeclamptic cases.

The cord blood selenium levels were significantly decreased in neonates born to cases with severe PET as compared with cord blood levels of neonates born to cases with non-severe PET for both low birth weights neonates *(p*=0.0134) and for normal birth weight neonates (*p*<0.0001).

The cord blood selenium levels were significantly higher in the normal birth weight groups as compared with cord blood of low birth weight groups in cases of severe PET (*p*= 0.0016) & in non-severe cases of PET *(p*= 0.0006).

## Discussion

Preeclampsia (PET) and intrauterine growth restriction (IUGR) may be due to oxidative stress [10]. It is thought that excessive production of reactive oxygen species (ROS) play a critical role as a possible mediator of endothelial cell dysfunction resulting in hypertension and clinical manifestations of preeclampsia [*11*]. The trace element selenium is an essential component of the antioxidant selenoproteins glutathione peroxidases. These remove the products of attack (ROS) by hydroxides and oxidized lipoproteins, and so limit adverse effects on the endothelium [*11*].

**In the present study**, the serum selenium was found to be significantly decreased in cases with preeclampsia as compared with the normal pregnants controls. This is in agreement with previous several studies showing that pregnant women with preeclampsia disease have selenium deficiency concentrations in comparison with normotensive women, and selenium deficiency is associated with PET [6, 12- 15].

*In the present study*, the cases with severe PET had significantly lower levels of selenium as compared with the non-severe PET. The results of the present study are in agreement with a previous finding that revealed a significant reduction in serum selenium in severe PET cases as compared with the non-severe PET cases [15].

Observational studies show that vitamins C and E or other antioxidants are lower in women who develop preeclampsia or IUGR [16].

Low plasma concentrations of selenium may be one etiology accounting for the higher incidence of preeclampsia and may suggest that selenium supplementation might lower the incidence of PET *[17].* Selenium supplementation has a direct capacity to increase the activity of endogenous antioxidant enzymes protecting placental tissue from oxidative damage.

Significant reductions in the incidence preeclampsia were found to coincide with increases in plasma/serum selenium concentration in the New Zealand and Finland populations. This supports the hypothesis that selenium supplementation may be beneficial in reducing oxidative stress in women at risk of preeclampsia [12].

The development of preeclampsia may be due to the reduced selenium concentrations that might adversely affect the functional activities of the seleno-proteins, leading to inability to protect against oxidative damages [18, 19].

There are several ways in which selenium in seleno-proteins could reduce the risk and severity of preeclampsia. Seleno-proteins protect the endothelium by controlling the cytokine induced adhesion molecule expression and by reducing inflammation [20].

*The results of the present study* revealed lower **serum cord selenium** levels in *low birth weight infants* born to cases with severe as compared with the normal birth weight neonates born to cases with severe preeclampsia. Also, the serum cord selenium levels were significantly lower in low birth weight neonates born to cases with non-severe preeclampsia as compared with the normal birth weight neonates born to cases with non-severe preeclampsia. The neonates born to cases with severe PET had significantly lower levels of umbilical cord selenium levels as compared with the neonates born to cases with non-severe PET. The results of the present study are in agreement with previous stud**ies** suggesting that the maternal serum selenium concentrations may have an effect on neonatal birth weight [21, 22].

During pregnancy the concentration of selenium in the blood of pregnant women decreases due to it transfer to the developing fetus. Maternal deficiency in selenium, copper and zinc concentrations during pregnancy were found to be associated with small-for gestational- age infants [23].

Some authors believe that women with low selenium level who are planning pregnancy or are in the initial period of pregnancy should be supplemented with **selenium** [24]. Selenium supplementation is suggested in cases with history of premature delivery to minimize or prevent clinical complications caused by prematurity [22]. Selenium has protective effect for neonates against neurotoxicity from prenatal manganese exposure. Selenium supplementation should be considered during pregnancy, especially in areas with low natural selenium [25].

## Conclusion

Early ante-natal care and treatment for pre-eclamptic women are recommended.

Selenium supplementation may prevent preeclampsia. Further studies are needed in different areas in Egypt and on large number of pregnant women to determine possible importance of dietary selenium supplementation as regards the prevalence of preeclampsia.

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## Conflict of interest

none.

## Contributions of the Authors

Each author had participated sufficiently to the work.

(1)- Ashraf A Foda: declares that he participated in the paper (by planning the design of study, clinical work and collection of samples, analysis and interpretation of data, drafting the article and revising its contents), and he approved the final version of the article to be published.

(2)- Engy A Foda: declares that she contributed to the work by planning the design of study, Laboratory analysis, analysis and interpretation of data, and revising its contents), and she approved the final article to be published.

(3)- Zeinab H.El-Said : declares that he participated in the paper (by planning the design of study, interpretation of data, revising the contents of the article), and approval of the final article to be published.

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