International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Original Research Article.

Evaluation of Total Oxidative Stress, Total Antioxidant Capacity Along with Selenium and Vitamin E Level among Saudi Women Experiencing Unexplained Recurrent Miscarriage and Intrauterine Foetal Death

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ABSTRACT

Introduction: Oxidative stress is integrated with declined female fertility. Our modern sedentary life style and exposure to toxins make vulnerable to body to increased amount of oxidative stress and lead to higher oxidative damage to DNA and may affect ova, sperm or the development of the embryo, leading to infertility, miscarriage and congenital defects. In the present study our aim was to assess the concentration of total oxidative stress, total antioxidant capacity, selenium and vitamin E level in women suffering from recurrent spontaneous miscarriage and intra uterine foetal death and compare levels with normal pregnant women.

Methods: In this cross-sectional study, a group of pregnant women (n= 82) at less than 10 weeks of gestation and a control group of healthy pregnancies with similar characteristics (n=85) were included.. Serum total antioxidant capacity and total oxidant status level were determined using Hitachi 912 analyzer whereas selenium level was measured fluorometrically and vitamin E level was determined by using HPLC.

Results: As compared with the control group, the Mean± SD value of maternal serum TOS level was significantly higher in study group patients (4.29 ± 0.67vs. 2.46 ± 0.52mmol Trolox Equiv./L; $p < 0.001$) whereas TAC value was recorded significantly lower (1.03 ± 0.22vs.1.86 ± 0.10mmol Trolox Equiv./L; $p < 0.05$). Vitamin E level and selenium level was significantly low statistically in study group patients (4.86 ± 0.21 vs. 9.23 ± 0.26 mg/l; ($p<0.001$) and (76.66 ± 1.63vs. 95.67 ± 1.83 ng/ml; ($p<0.001$) respectively at the level of 1%. The mean ± SD value of TOS, TAC, vitamin E and Selenium in two different sub categories of study group shows no any statistical significant difference for all included parameters.

Conclusion: Increased total oxidative stress and low TAC level along with low level of vitamin E and selenium might be a significant reason of recurrent miscarriage.

Keywords: Total Oxidative Stress, Total Oxidant Capacity, Intrauterine Foetal Death, Recurrent Spontaneous Miscarriage.

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Article History:
Received: 06-07-2018, **Revised:** 01-08-2018, **Accepted:** 21-09-2018

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2018.4.5.035	

INTRODUCTION

Reactive oxygen species (ROS) are substances with one or more unpaired electrons; therefore highly reactive and interact with lipids, proteins or DNA, leading to oxidation and cellular malfunction that may initiate pathological processes. ROS can be generated through many pathways within cells, but the mitochondria, ER and enzymes such as NADPH oxidase are the most important sources. These pathways can respond to a variety of stimuli, but arguably the most important ones for pregnancy are perturbations in the maternal blood supply to the placenta and inflammation. In some research studies it has also been mentioned that the etiology of recurrent pregnancy loss is multifactorial and involves genetic and environmental factors.[1]

In a healthy body, ROS and antioxidants remain in balance. When the balance is disrupted towards a superfluity of ROS, oxidative stress(OS) arise. Oxidative stress, which is also defined as an imbalance between pro-oxidants and antioxidant capacity, has been implicated in suboptimal reproductive performance from the earliest stages of development to labor and delivery .It plays a role in both the normal development of the placenta as well as in the pathophysiology of complications such as miscarriage, preeclampsia, intrauterine growth restriction (IUGR), and premature rupture of the membranes. Increased oxidative stress in the placenta of women with PE and IUGR has been well documented.[2] Oxidative stress has also been acknowledged as the main driving factor in placental apoptosis, releasing placental contaminants in to the mother's bloodstream. It is considered to be a crucial pathogenic process in the development of PE.[3]

The literature provides some evidence of oxidative stress influencing the entire reproductive span of a woman, even the menopausal years. It plays a role in multiple physiological processes from oocyte maturation to fertilization and embryo development. Numerous studies have supported the theory of insufficient blood supply to the placenta, modulating the mother's metabolism, inflammation, and oxidative stress. This, in turn, leads to complications during pregnancy.[4] Apart from the damage caused to gametes, there is some probability that oxidative stress and system inflammation in the mother's circulatory system may both be responsible for the basic complications – related anomalies. This is because genome instability may alter the phenotypes of cells and eventually decrease their proliferative potential, leading to complications related to abnormal placenta development. Furthermore, abnormal placenta development gives rise to hypoxia and reperfusion as a consequence of ischemia. As a result, the production of cytokinesis stimulated, generating dysfunctions in the endothelial cells that play an important role in the development of pregnancy complications.[5]

The body's complex antioxidant system is influenced by dietary intake of antioxidant like vitamins and minerals such as vitamin C, vitamin E, selenium, zinc, taurine, hypotaurine, glutathione, beta-carotene, and carotene.[6] Glutathione is existing in the oocyte and tubal fluid and has a role in enhancing the development of the zygote beyond the 2-cell block to the morula or the blastocyst stage.[7] Selenium is an essential component of the selenoproteins especially glutathione peroxidase required for normal health and reproduction. It play an important role in cellular antioxidant defense by reducing lipid hydro-peroxides to their corresponding unreactive alcohols and reducing free hydrogen peroxide to water.[8] The requirement of selenium is increased in pregnancy as a result of transport to the growing foetus. In the recent years, some studies suggested that spontaneous abortion in women might be related to selenium deficiency.[9]

In few recent research studies it has been concluded that alpha tocopherol (Vitamin E) level was considerable low in the cases of recurrent spontaneous miscarriage. There might be an association between essential micronutrient selenium, Vitamin E status and miscarriage, which may suggest a different approach for preventing oxidative stress.

In the present research study, we focused at determining the serum level of total oxidant status (TOS), total antioxidant capacity (TAC), vitamin E and selenium level in pregnant women with history of recurrent pregnancy loss and intra uterine fetal death (IUFD).

MATERIALS AND METHODS

This cross-sectional study was carried out in 167 pregnant women attending the obstetrics and gynecology clinic of the department of Obstetrics and Gynecology, King Saud Medical City Hospital, Riyadh, KSA for their normal checkup. This research study was approved by the Medical Ethics Committee of the King Saud University, Riyadh, KSA and informed consent was obtained from all the participants. Gestational age was evaluated on the basis of the last menstrual period and confirmed by ultrasound. Patients were divided into two groups.

1. **Study Group:** The study group included 82 pregnant women at less than 10 weeks' gestation which were subdivided in two groups.
   A. 50 patients having history of recurrent spontaneous miscarriage.
   B. 32 patients were selected with history of recurrent intrauterine foetal death.
2. **Control Group:** The second group consisted of 85 patients at less than 10 weeks of gestation with normal ongoing pregnancies with no pre-existing complications.

All of the control group patients were matched for age, gestational age and body mass index (BMI).

Exclusion Criteria

History of documented chromosomal abnormalities, Endocrine diseases, Internal diseases, Connective tissue diseases, Hypertension, Coagulopathies, Multiple pregnancies, Smoking, Diabetes mellitus, and anemia.

Collection of Samples

Ten ml of venous blood sample was taken using new disposable pyrogen free needles and syringes with minimal stasis. Blood was collected in a plain tube and kept for 1–2 hours on the desk to clot. Serum was separated by centrifugation at 4000 g for 10 minutes and frozen at -70˚C for later analysis.

Demographic Indices

The demographic characteristics were age, age at menarche, parity, length of menstrual cycle, number of live births, number of previous pregnancies and diet history.

BIOCHEMICAL ANALYSIS

Measurement of Total Antioxidant Capacity

Serum TAC was determined by HITACHI 912 automatic analyzer using an automated measurement method. In this method, hydroxyl radical is produced. Ferrous ion solution, which is present in a reagent, is mixed with another reagent having hydrogen peroxide. During reaction brown-colored dianisidinyl radical cation are released that measure the antioxidative effect of the sample against the dynamic free radical reactions. The results are expressed as m mol trolox equiv/l.

Measurement of Total Oxidant Status

Serum TOS was determined by HITACHI 912 automatic analyzer using a novel automated measurement method. Oxidants oxidize the ferrous ion-o-dianisidine complex to ferric ion. Glycerol molecules raise the oxidation reaction. In an acidic medium, the ferric ion formed a colored complex with xylenol orange. Hydrogen peroxide is used for the calibration, and the results are expressed in terms of m mol trolox equiv./l.

Measurement of Serum Tocopherol

Serum tocopherol (vitamin E) was estimated by high performance liquid chromatography HPLC) (Waters, USA).This is a separation process whereby a mixture of solutes dissolved by another differential distribution of the solutes between two different phases. Serum sample was treated with ethanol to separate out some interfering components after that tocopherol was separated on Waters symmetry C18 column (3.9mm x 150 mm with waters symmetry C18 (3.9mm x 10mm) guard column between an initial mobile phase of acetonitrile in water and then acetonitrile. The flow rate was 1 ml/min. The concentration of Vitamin E was calculated in mg/L.

Measurement of Selenium

The selenium concentration in whole blood and plasma was measured fluorometrically with 2, 3-diaminonaphthalene. The mean level of selenium in the reference whole blood sample was 81.7 ± 2.5 ng/mL and in serum was 84.5±2.4 ng/mL, while the certified concentrations were 83 and 86 ng/mL respectively.

Statistical Analysis

The data were carefully entered, checked and properly coded into Microsoft excel software package on a personal computer (PC). The data were subsequently transferred to Statistical Package for Social Scientists (SPSS) version 16 for the statistical analysis. Student's (t)-test was used for the comparison of x ± S.D at 95% confidence level. A $p<0.05$ was considered significant.

Table 1: Baseline characteristic's and output data of study group (82 cases) and control group (85 cases) women.

Characteristic's	Study group (N= 82)	Control group (N=85)	P value
Age(Years)	31.29 ±0.69	30.90 ±0.82	0.364
LMC (Days)	28.02 ±0.61	28.32 ±0.19	0.470
AM(Years)	12.98 ±0.36	13.01 ±0.22	0.071
NLB	0.35 ±0.16	2.51 ±1.36	1.577
NPP	3.39 ±0.21	2.22 ±0.10	5.043
Gestational age(Weeks)	8.02 ±1.36	8.49 ±3.50	0.125
BMI (kg/m²)	26.91 ±3.5	24.76 ±4.02	0.403
Hb(%)	114 ±0.95	116 ±2.02	0.896

LMC= length of menstrual cycle, AM= Age at menarche, NLB= Number of live birth,
NPP= Number of previous pregnancies, BMI= Basel metabolic Index

Table 2: Baseline characteristic's and output data of study group patients (82 cases of RM and IUFD) divided in two groups.

Characteristic's	Abortions (N=50)	IUFD (N=32)	P value
Age (Years)	28.1 ±4.6	29 ± 4.9	0.134
Weight (KG)	65.9 ±7.3	69.0 ± 6.7	0.312
Height(cm)	164 ± 6.2	163 ± 3.7	0.138
BMI (kg/m²)	26.7 ± 3.4	27.6 ± 4.1	0.168
HB (%)	10.9 ± 0.88	11.9 ± 0.86	0.813

Table 3: Mean level of Total oxidant stress, total antioxidant capacity, vitamin E level and selenium level in study and control group women.

Markers	Study group N=82 (mean value ±SD)	Control group N= 85 (mean value ±SD)	P VALUE
Total oxidant stress (TOS) (m mol trolox equiv./l)	4.29 ± 0.67	2.46 ± 0.52	<0.001*
Total antioxidant capacity (TAC) (m mol trolox equiv./l)	1.03 ± 0.22	1.86 ± 0.10	<0.05**
Vitamin E (mg/l)	4.86 ± 0.21	9.23 ± 0.26	<0.001**
Selenium (ng/ml)	76.66 ± 1.63	95.67 ± 1.83	<0.001**

n=number of Subjects, mg/l= milligram per litre, ng/ml= nanogram per millilitre
* - Significance at 5% level (more than 1.96)
** - Significane at 1% level (more than 2.57)

Table 4: Mean level of Total oxidant stress, total antioxidant capacity, vitamin E level and selenium level in study group women divided in two groups.

Markers	Abortion (N= 50)	IUFD (N=32)	P VALUE
Total oxidant stress (TOS) (m mol trolox equiv./l)	4.63 ±0.83	3.95 ±0.51	0.70
Total antioxidant capacity (TAC) (m mol trolox equiv./l)	0.95 ±0.23	1.12 ±0.21	0.55
Vitamin E (mg/L)	4.26 ± 0.22	5.46 ±0.20	4.04
Selenium (ng/ml)	74.29 ± 1.26	78.76 ± 2.40	1.76

RESULTS

Details of baseline characteristics were recorded and analyzed in the study and control group. There were no statistically significant differences regarding maternal age, gestational age, length of menstrual cycle (LMC), age at menarche(AM), percentage of Hb and BMI ($p>0.05$). While, there were statistically significant differences ($p<0.05$) in the mean values of number of previous pregnancies (NPP) and number of live birth (NLB) were calculated. (Table 1)

Some baseline characteristic's like age, weight, height, BMI and Hb(%) of study group patients which were sub grouped as 50 cases of abortion and 32 case of IUFD were also analyzed statistically and there were no any statistical difference observed.(Table 2)

As compared to healthy control group patient, mean± SDvalue of maternal serum TOS level was significantly higher in study grouppatients(4.29 ± 0.67vs. 2.46 ± 0.52mmol Trolox Equiv./L; $p< 0.001$). The value is significant at the level of 5%, whereas mean± SD value of TAC was recorded as significantlylower in study group patientsas (1.03 ± 0.22vs.1.86 ± 0.10mmol Trolox Equiv./L; $p<0.05$). The value is significant statistically at level of 1%.

Mean± SD value ofVitamin E wassignificantly low in study group patients as compared to control group (4.86 ± 0.21 vs. 9.23 ± 0.26 mg/l; ($p<0.001$). The value is significant statistically at the level of 1%. Whereas mean± SD value of selenium level was considerable low (76.66 ± 1.63 vs. 95.67 ± 1.83 ng/ml; ($p<0.001$)in study group as compared to control group patients. The result was significant statistically at 1% of level (<0.001). (Table 3) The mean ± SD value of TOS, TAC, vitamin E and Selenium were also compared in two different sub categories of study group. There were no any statistical significant difference was observed in two subcategories of study group for all these parameters. (Table 4)

DISCUSSION

Present study was designed to study the level of total oxidant stress and total antioxidant level along with selenium and vitamin E level in patients suffering from recurrent spontaneous miscarriage or intrauterine foetal death and compared the results with normal pregnant females.

The Oxidative stress is a deleterious process that damages cell structures as well as responsible for cellular structural changes. The presence of ROS within the ovary especially during the ovulation process and in the endometrial surface has significant physiological and pathological implications in the female reproductive tract. It seems that physiological levels of ROS are required as modulators of a large spectrum of female reproductive pathways such as oocyte maturation, ovarian steroidogenesis, corpus luteum functions, ovulation and are involved in the processes of fertilization, embryo development and pregnancy. Conversely, abnormal increased ROS activity is negatively correlated with oocyte development, embryonic development and pregnancy outcome.[10] Natural enzymatic antioxidants such as catalase, glutathione peroxidase and superoxide dismutase as well as non-enzymatic antioxidants (vitamin A, vitamin E, zinc and selenium) are essential in maintaining adequate levels of ROS in the cell by preventing and removing excess of free radicals.[11]

Oxidative stress and loss of oxidant defense has been implicated as an important cause of recurrent pregnancy loss in some research studies.[12] It may result from premature oxygenation of the early embryonic environment.[13] In a research study researchers showed an increase in markers of oxidative stress in placental tissue formerly pregnancy losses compared with controls and suggested that increased ROS generation may be due to premature establishment of maternal placental perfusion.[12] Some biochemical markers of ROS like lipid peroxidation products reached at high levels immediately before abortion in a research study.[14]

In our research study also we observed significantly increased level of ROS in study group patients same like other researchers.

Since ROS are highly reactive, it is essential that antioxidants be near the site of ROS production, so they can be quickly activated and will be effective in preventing ROS-induced damage.[15] The developing embryo can generate both intracellular and extra-cellular ROS, thus requiring effective antioxidant activity. Enzymatic antioxidant defenses have been documented in mammalian embryos and oocytes[16] and nonenzymatic defenses in tubaland follicular fluids.[17] Increased levels of antioxidants have been documented in normal pregnancy.[18] Whereas loss of antioxidant defenses have been observed in patients with recurrent abortion.[19] The lower antioxidant levels could aggravate pro-oxidant injury on endothelial cells, altering prostacyclin–thromboxane balance and culminating in preeclampsia or abortion.[20] The impact of the glutathione/glutathione transferase system has been particularly studied with regard to the occurrence of abortion, without excluding associated genetic polymorphisms.[21] Animal studies have demonstrated the protective effects of glutathione peroxidase against oxidative damage in neurogenic tissue development in fetuses.[22] Similar findingswere recorded in our present research study. Patients who were suffering from recurrent pregnancy loss and intra uterine foetal death having high amount of ROS and low level of total antioxidant capacity as compared with controls The results are totally in agreement with other researchers that oxidative stress might be a significant factor for recurrent miscarriage in those patients.

Oxidative stress is generated during normal placental development. Some micronutrients function as essential co-factors or antioxidants. Insufficient supply of antioxidants could exaggerate oxidative stress within both the placenta and maternal circulation with adverse pregnancy outcomes.[23] The importance of adequate micronutrient intake during periconceptional and pregnancy periods has been reported in a research study.[24] Depletion of antioxidant capacity, whether through a low abundance of non-enzymatic or enzymatic antioxidants renders the cell vulnerable to oxidative attack, even under physiologic situations where redox status is maintained through a careful balance of a low level of ROS synthesis and the pathways of cellular defense.[25] Antioxidants including vitamins C and E and antioxidant cofactors such as selenium, zinc, and copper are capable of disposing, scavenging, or suppressing the formation of ROS. There are few studies focusing on the role of antioxidants in female infertility in the past few years. Few studies has suggested that miscarriage may be related to selenium deficiency.[26,27] However, a direct relationship between selenium deficiency and abortion has not been established to date. Although a deficiency state has been found in various tissues in patients undergoing abortion, the exact mechanism has not yet been identified.[28] Follicular fluid contains high levels of antioxidants, which protect oocytes from ROS-induced damage. Significantly lower selenium levels were detected in follicular fluid of patients with unexplained infertility compared with those with tubal infertility or couples with male factor infertility.[29]

During pregnancy the requirement for selenium is increased as a result of the transport of this element to the growing fetus.[30] In two different research studies, it was observed that the selenium concentrations in whole blood and plasma, as well as the activity of glutathione-Px in red cells and plasma, are significantly lower in women at delivery, compared with non-pregnant women.[31]

Our results are also similar and in favor of all these research studies. We determine low level of selenium in the serum of our study group patients. Whereas in two different published research studies, investigated the association of selenium status with recurrent abortion indicated no significant differences in the levels between patients and controls.[32] In contrast to our study, significant increased serum selenium level in pregnant women with history of recurrent spontaneous abortion compared with healthy normal pregnant women were observed in some research study.[33] This is also contrary to the findings by others.

Vitamin E is one of the most potent non-enzymatic antioxidant. Researchers reported that because of the lipophilic property of the tocopherol molecule, vitamin E is the major free radical chain terminator in the lipophilic environment. Various research studies have shown that adequate intake of vitamin E in pregnant women enhances term delivery and has been shown to protect and sustain the endometrial membrane from free radicals. Its deficiency has been associated with foetal death.[34] According to a new research led by the Johns Hopkins Bloomberg School of Public Health, Pregnant women in Bangladesh with low levels of the most common form of vitamin E (Alpha tocopherol) are nearly twice more likely to have a miscarriage than those with adequate levels of the vitamin in their blood.[35]

In an another research study, patients suffering from unexplained recurrent miscarriage had decreased concentrations of plasma vitamin C and vitamin E and increased concentration of oxidative stress.[36] The role of antioxidants and lipid peroxidation in RPL was studied in a clinical research study and suggested that the significant decrease in vitamin E levels caused the significant increase in MDA level in RPL women.[37] Increased level of lipid peroxidation and significantly reduced amount of glutathione, vitamin A, E and beta carotene were observed in women with habitual miscarriage.[38] Our results were also in agreement of all these research study as vitamin E level was observed low in women suffering from repeated miscarriage.

CONCLUSION

The role of oxidative stress in female fertility is an understudied and compelling area for investigation, but one that is expanding rapidly. It is increasingly apparent that ROS play a central role in many signal transduction pathways. As the etiology of recurrent pregnancy loss remains unclear and is a scientific challenge therefore Identifying modifiable factors to decrease oxidative stress, increase antioxidant capacity and routine checkup of vitamin E and selenium level in the gynecologic environment may be an inexpensive and noninvasive therapy for increasing fertility. In other hand ROS levels in follicular fluid may be used as markers for predicting the success of in vitro fertilization (IVF).

ACKNOWLEDGEMENT

The authors are very thankful to be supported by grant from the Research Centre of the “Centre for Female Scientific and Medical colleges”, Deanship of scientific research, King Saud University, Riyadh to carry out the research. There was no any conflict of interest for this study.

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Source of Support: Nil.

Conflict of Interest: None Declared.

Cite this article as: Poonam Tyagi, Noura Al- Dayan, Abeer Ali El Sherbiny Ateya. Evaluation of Total Oxidative Stress, Total Antioxidant Capacity Along with Selenium and Vitamin E Level among Saudi Women Experiencing Unexplained Recurrent Miscarriage and Intrauterine Foetal Death. Int J Med Res Prof. 2018 Sept; 4(5):148-53. DOI:10.21276/ijmrp.2018.4.5.035