

ROLE OF ANTI-OXIDANT SUPPLEMENTATIONS IN RECURRENT EARLY PREGNANCY LOSS

By

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ABSTRACT

Background: Early pregnancy loss is defined as loss of an intra_uterine pregnancy within the first trimester.

Objective: To detect role of anti-oxidant supplementations in women with early pregnancy loss.

Patients and methods: This clinical trial was conducted at Al-Azhar University, maternity Department, Assuit from January to March 2019. In this study, we selected a group of pregnant women (100) with history of recurrent early pregnancy loss up to 12 weeks. They were divided in to two equal groups (group A) received antioxidants supplementation (zinc, selenium, vitamin c and vitamin E) whereas (group B) received placebo. After procedure follow up of pregnant women was done.

Results: In Group A, no significant relation between continuation of pregnancy and age of the mother, gestational age by date, gestational age by U/S, number of abortion and BMI, whether patient get pregnant naturally or by induction. In Group B, no significant relation between continuation of pregnancy and age of the mother, gestational age by date, gestational age by u/s, number of abortion, and BMI get pregnant naturally or by induction. Comparison of the Outcome of pregnancy beyond 12 weeks in the two study groups, in group A was 40 (80%) and 25 (50%) in group B with significant difference.

Conclusion: Continuing pregnancy with antioxidants supplementation was more than those who received placebo (folic acid only).

Keywords: Anti-Oxidant Supplementations, Pregnancy Loss.

INTRODUCTION

The Practice Committee of the American Society for Reproductive Medicine (*Practice Committee of the American Society for Reproductive Medicine, (2012)*) defines recurrent pregnancy loss as by two or more failed clinical pregnancies.

Sporadic miscarriage occurs before embryo development could represent a physiological phenomenon, which prevents congenitally malformed or chromosomally abnormal embryos to

progress to viability. Chromosomal abnormalities incompatible with life observed in 85% of early clinical miscarriages, and chromosomal aberrations are responsible for 29-60% of RM (*Kurahash et al., (2012)*).

Oxidative stress has also been implicated as an important cause of recurrent pregnancy loss. Loss of antioxidant defenses have been shown to be associated with recurrent pregnancy loss. Biochemical markers of ROS-induced membrane damage such as lipid

peroxidation products, reach high levels immediately before abortion. It has been proposed that an oxidant/antioxidant imbalance is associated with pregnancy loss (*Liu et al., 2018*).

Alcohol increase the risk of miscarriage significantly, and the national Danish birth study, suggested that the risk increased in a dose related manner (*Andersen et al., 2012*). A systematic review investigating the relation between miscarriage, and obesity after spontaneous conception, showed significant association between obesity, and both sporadic and RM (*Boots and Stephenson, 2011*).

Maternal and child health is a matter of concern all around the world but in developing countries, the situation is much worse. This is mainly due to lack of education and resources made available to mothers. These do not only result in poor maternal and child health but also often result in Recurrent Pregnancy Loss (RPL).

The mothers in such cases are often malnourished and unable to provide needs of the developing fetus that is completely dependent on the mother for its growth. This deficiency of micronutrients in mother risks the health and life of both, the mother and the fetus (*Suryawan and Rahardjo, 2013*). Thus, it is crucial to understand the role of antioxidant micronutrients in influencing successful outcome of pregnancy and improving maternal health.

The aim of this study was to detect role of anti-oxidant supplementations in women with early pregnancy loss.

PATIENTS AND METHODS

This clinical trial was conducted at Al-Azhar University, maternity Department, (Assiut) from January to march 2019.

Study design:

The patients were recruited from women attending outpatient clinic suffering from recurrent pregnancy loss.

Inclusion criteria:

Age 20-30 years, BMI₂₂₋₂₈kg/m², First trimester pregnancy (clinically detected pregnancy), History of two or more early pregnancy loss, No history of uterine anatomical abnormalities, Anti-Phospholipid antibody syndrome or maternal infection.

Exclusion criteria:

Pregnancy beyond 13 weeks, History of clinical medical disorders, Anti-phospholipid antibody syndrome, Thrombophilias, History of polycystic ovary syndrome. Exclusion of maternal infection "TORCH" Anti – phospholipid antibody syndrome, DM, Hypertension, thrombophilia.

An approval of the study was obtained from Al- Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance to share in this work.

The study was designed as prospective double blind randomized controlled study of 100 women, divided into two equal groups:

Group A received anti - oxidants supplementation (oral preparation containing selenium, Zinc, Vit C, Vit E.) and folic acid 500 microgram, and

Group B received placebo. (folic acid 500microgram).

All Cases were subjected to: Full history, general and abdominal examination, trans – vaginal " ultrasonography and follow up every two weeks using trans vaginal ultrasonography (Sonoscape S12) to detect foetal viability, fetal growth and calculate gestational age, development of the placenta) until 12th weeks of pregnancy.

Outcome measures: Pregnancy continued beyond 12th weeks and occurrence of abortion (missed abortion, blighted ovum)

Criteria of missed abortion:

Missed abortion was defined if the crown rump length (CRL) was more than 6mm and there was no embryonic cardiac activity

Criteria of Blighted ovum. Mean gestational sac diameter was more than 20 mm and no yolk sac or embryonic pole.

Statistical analysis:

Analysis of data was done using SPSS (Statistical Package for Social Science) statistical software, v. 22, Echo soft corp., USA, 2004.

Methods of presenting data and tests used for comparison Mean ± Standered Deviation, P value < 0.05 was considered significant.

Linear regression test .Chi 2 test

RESULTS

The present study was carried out on 100 individuals. They were divided into two equal groups: group A: (patients received antioxidants supplementation) and group B: (placebo not received antioxidants supplementation).

Table (1) showed a comparison between two study groups A&B as regard age of mother gestational age by date, gestational age by u/s. number of abortions, and BMI. It showed no significant difference between them. Comparison between group A&B as

regard get pregnant naturally or by induction. Most of them in both groups get pregnant naturally.no significant difference between them. In both groups no significant difference as regard number of previous CS and history of previous gynecological operation. Comparison of the Outcome of pregnancy beyond 12 weeks in the two study groups in group A was 40 (80%) and 25 (50%) in group B with significant value <0.001. So, use of antioxidants greatly increased the chance of continuation of pregnancy.

Table (1): Patients' characteristics in the two study groups

| Demographic data. | Group(A). N(50). | | | Group(B). N(50). | | | P-value. |
|--|-----------------------|----|----|-----------------------|----|----|----------|
| | Mean±SD | N | % | Mean±SD | N | % | |
| 1- Age of mother | (20-30) 26.98±3.63 | | | (20-30) 27.40±2.88 | | | > 0.05 |
| 2- Gestational age by date | 7.36±1.50 | | | 7.40±1.36 | | | > 0.05 |
| 3- Gestational age by u/s | 7.46±2.06 | | | 7.34±1.98 | | | > 0.05 |
| 4- Number of abortions | 2.80±1.55 | | | 2.90±1.34 | | | > 0.05 |
| 5- BMI | 23.54±1.49 | | | 23.66±1.44 | | | > 0.05 |
| 6-Get pregnant naturally | | 90 | 45 | | 82 | 41 | > 0.05 |
| 7-Get pregnant by induction | | 10 | 5 | | 18 | 9 | > 0.05 |
| 8-Number of Previous CS | | 20 | 10 | | 22 | 11 | > 0.05 |
| 9- Previous gynecological operation | | 4 | 2 | | 4 | 2 | > 0.05 |
| 10-Continued pregnancy beyond 12 weeks | | 40 | 80 | | 50 | 25 | <0.002 |

Table (2) showed in Group B, no significant relation between continuation of pregnancy and age of the mother, gestational age by date, gestational age by U/S, number of abortion, and BMI.

Group B, as regard continuation of pregnancy there was no significant difference whether patient gets pregnant naturally or by induction. Also, history of previous CS or previous gynecological

operation didn't have effect on continuing pregnancy. Comparison of the pregnancy loss in the two study groups in group A 10 cases were aborted 9 of them was diagnosed as missed abortion, and one case diagnosed as blighted ova, while in group B, 23 cases diagnosed as missed abortion, and 2 cases diagnosed as blighted ova with a significant value <0.001.

Table (2): Relation between Continued pregnancy beyond 12 weeks and Patients' characteristics in group B

| Continued pregnancy beyond 12 weeks | f | | p- value |
|-------------------------------------|--------------------|--------------------|----------|
| Group B | | | |
| 1. Age (Years): | 00.728 | | > 0.05 |
| 2. Gestational age by date | -3.492 | | > 0.05 |
| 3. Gestational age by u/s | 9.258 | | > 0.05 |
| 4. Number of abortion | -0.923 | | > 0.05 |
| 5. BMI | 1.297 | | > 0.05 |
| 6. Get pregnant naturally | 1.992 | | > 0.05 |
| 7. Get pregnant by induction | -2.107 | | > 0.05 |
| 8. Number of Previous CS | 1.808 | | > 0.05 |
| 9. Previous gynecological operation | -0.619 | | > 0.05 |
| Pregnancy loss | Group A: "n=50" | Group B: "n=50" | P-value |
| | N | N | |
| Missed abortion | 9 | 23 | > 0.05 |
| Blighted ova | 1 | 2 | |

Linear regression test was used. Chi 2 test was used.

DISCUSSION

In the present study, our main goal was to assess and compare the efficacy of antioxidants supplementation can positively affect the health of the mother and child and their survival.

In our study, Patients' characteristics data were compared between the 2 groups. it was found that no significant differences in age of mother (year), number of abortion, BMI, gestational age (by date) and gestational age by U/S .

Our results demonstrated that, the means age in group I and II of 26.98± 3.63 years and 27.40± 2.88 years respectively (p=0.838). The age in group I and II ranged between 21-32 years and 20-35 years with means of 26.29 ± 3.79 years and± 4.53 years respectively.

A similar pattern of results was obtained in the study published on the Pak Armed Forces Med Journal 2017, which was carried over 123 pregnant women

divided in group 1 received antioxidant (n=63) and group 2 received placebo (n=54) (The Antioxidants tablets contained vitamin C 500mg, vitamin E 300 mg and Selenium (Se) 100 mg micrograms. Whereas Placebo contained lactose of 900 mg only for per day consumption according to for pregnant women formulated by the gynecological expert): It was found that the chances of any outcome, whether positive or negative, were much higher for the experimental group. Mother that received antioxidants were more likely to conceive and give birth to a healthy baby compared to the controlled group (*Bhatti and Thaver, (2017)*).

Regarding the gynecologic and obstetric history between studied groups, it was found that no statistically significant difference in get pregnant naturally, getting pregnant by induction, number of previous caesarian section, and previous gynecological operation.

In the present study, pregnant women received antioxidants supplementation, 90% of them with get pregnant naturally, 80% of them were no previous CS, 96% of them with no history of previous gynecological operation and while pregnant women received placebo (folic acid) (82% of them were get pregnant naturally, 78% of them were no previous CS, 96% of them with no history of previous gynecological operation.

Our results demonstrated that, the women who were administered antioxidants in the studies showed improvement in chances of outcome and statistically significant difference on continued pregnancy in compared with placebo group.

In the current study, pregnant women received antioxidants supplementation (80%) of them were continued pregnancy while (20%) of them were loss their pregnancy. However, it was noticed that (50%) of the pregnant women receiving placebo lost their pregnancy and (50%) continued pregnancy.

In many studies found that increased free radical activity has been implicated in the pathogenesis of recurrent abortion. The relation between recurrent abortion and OS is not only contributed by the increase in ROS generation seen in early pregnancy but also associated to increased levels of antioxidants needed to neutralize and scavenge excessive ROS present in women with habitual abortion (*Victor et al., (2016)*).

Mistry and Williams, (2011) evaluated the outcome of deficient antioxidant defense in women with habitual abortion and demonstrated elevated lipoperoxides and significantly decreased vitamin A, E,

and beta carotene in this population compared with the control group. This finding confirmed that OS may be involved in the pathogenesis of recurrent abortion.

Victor et al., (2016) studied changes in antioxidant levels by measuring SOD levels, which measure the amount of oxygen ion scavenger that may result in increased ROS production. This study found that SOD levels were significantly lower in women with miscarriage than in healthy pregnant women.

In a normal pregnancy, vitamin E level naturally increases, while in an abnormal pregnancy, vitamin E concentrations are lower. Moreover, vitamin C levels increase physiologically during pregnancy. These occurrences suggest that perhaps vitamins C and E may play a role in compensating for the oxidative burst during early pregnancy, reducing the risk of pregnancy loss.

However, it is necessary to perform an accurate assessment of the appropriate type and dosage of vitamins that can be tolerated without causing deleterious side-effects to the mother and baby *Thaker et al., (2019)*.

Thaker et al., (2019) reported that trace metals such as Zn and Cu have a positive role in pregnancy outcome and optimum levels of Zn and Cu might be able to decline the chances of abortion occurrence in addition to other factors. The ratio of Cu/Zn has a positive role in reproductive outcomes.

This can also be used to explain why women who received antioxidant supplements had a higher chance to give birth to healthier infants in RPL and

normal trimester groups than did women who did not receive antioxidants.

CONCLUSION

Continuing pregnancy with antioxidants supplementation is more than those who received placebo (**folic acid only**).

Conflicts of interest

There are no Conflicts of interest.

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دور مضادات الأكسدة في حالات فقدان الحمل المبكر المتكرر

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خلفية البحث: يعرف فقد المتكرر المبكر للحمل بأنه فقدان إثنين أو أكثر من الحمل في الشهور الثلاثة الأولى من الحمل.

الهدف من البحث: تقييم ومقارنة فعالية مضادات الأكسدة في المرضي الذين يعانون من فقدان مبكر متكرر للحمل.

المریضات وطرق البحث: في هذه الدراسة تم إختيار مائة من الحوامل الذين يعانون من فقدان متكرر للحمل قبل الأسبوع الأثني عشر.

وتم تقسيمهن إلي مجموعتين متساويتين مجموعة أ تناولن الفيتامينات المضادة للأكسدة بينما مجموعة ب تناولن اقراص حمض الفوليك ثم تقييمهن ومتابعتهن.

نتائج البحث: تزداد احتمالية إستمرار الحمل مع تناول مضادات الاكسدة عن هؤلاء السيدات في المجموعة الاخری.

الاستنتاج: إعطاء السيدات الفيتامينات التي تحتوي علي المواد المضادة للأكسدة في بداية الحمل يمكنه ان يقلل من مخاطر فقدان الحمل المتكرر، ويزيد إستخدام المواد المضادة للأكسدة قبل الإخصاب من فرصة الحصول علي جنين سليم.