ROLE OF ANTIOXIDANT IN RECURRENT PREGNANCY LOSSES

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ABSTRACT

Objective: To compare the rate of recurrent abortion in antioxidants supplemented and non-supplemented mothers.

Study Design: Randomized control trail, double blind study.

Place and Duration of Study: Liaquat University Medical and Health Sciences-Jamshoro (LUMHS), Shaheed Mohtarma Benazir Bhutto Medical University Larkana (SBBMU) hospital and PMC hospital Nawabsha (2012-2014).

Material and Methods: The patients were the mothers who had aborted three consecutive losses continuously. It was multicentre hospitals based study, where cases of recurrent abortion mothers frequently reported and were available. Two techniques were used convenient and snowball to select the patients.

Results: A total of 123 cases of recurrent abortion (RA) were recruited and identified for registration (Point Estimate of Incidence) among them n=67 mothers in the active arm and n=56 in placebo arm. The R.A incidence rate was 89 per 1000 mothers at risk in Placebo arm and 149 per 1000 mothers at risk in Active arm. In case of RA the mean age was 30 years in both the arms. Mothers who had suffered recurrent abortion in both arms were mostly illiterate (61%). The mean duration of marriage in active arm was 16.7 years. Researcher found that most of mothers, 92 (75%) did not become pregnant after taking the prescribed supplementation.

Conclusion: The use of antioxidants before conception and during pregnancy significantly improves the chances of live births and outcome in general.

Keywords: Antioxidants, Recurrent pregnancy losses.

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INTRODUCTION

Recurrent pregnancy loss (RPL), recurrent miscarriage, or habitual abortion is defined as "the occurrence of three or more miscarriage of a fetus before 20 weeks of gestations (i.e. before fetus can live outside the womb)[1] has been reported to be about 2% of women. Based on the data which is presently available, the risk of RPL is 30% after 2 losses while after 3 losses, it increase to 33%[2]. In the first trimester, up to 20% of all the pregnancies are at risk of abortion but this risk significantly decreases in the second trimester[3]. Chromosomal abnormalities have been identified as one of the contributing factors in Spontaneous Pregnancy Loss (SPL); some sort of chromosomal abnormality is present in 50% of all morphologically normal looking embryos[4].

The two important factors of SPL remain age of mother and the successful outcome of last pregnancies[5]. As age of the mother increased, the risk of chromosomal abnormality and mis-carriage also increase making it an important factor in Recurrent Pregnancy Loss (RPL)[6,7]. RPL is therefore defined as "the occurrence of three or more miscarriage of a fetus before 20 weeks of gestations (i.e. before fetus can live outside the womb)"[8].

Most of the losses in human reproduction take place even before the implantation as up to 50% of losses occur during that time[9]. It is an established fact that intake of nutrients before and during the pregnancy significantly improves the health of the mother and the fetus[10]. Then again, insufficiency of supplements can prompt a bather for supplements and vitamins between the mother and the baby which can hurt health of

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both[11]. In order to keep the body of the mother strong and healthy, intake of antioxidants (as part of the nutrients) is very important which help in fighting germs and repairing cell bodies that get damaged during pregnancy[12].

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

Table-I: Showing demographics characteristics of participants.

Variable	Active n=67 (%)	Placebo n=56 (%)	Total (%)	*p*-value
Age (Years)				
15-25	6 (9.0)	10 (17.9)	16 (13.0)	
26-30	34(50.7)	29 (51.8)	63 (51.2)	0.429
31-35	23 (34.3)	14 (25.0)	37 (30.0)	
36-40	4 (6.0)	3 (5.4)	7 (5.9)	
Parity				
0	58 (86.5)	47 (83.9)	105 (85.3)	
1	2 (2.9)	3(5.3)	5 (4.0)	0.92
2	3 (4.4)	3 (5.3)	6 (4.8)	
3+	4 (5.9)	3 (5.3)	7 (5.9)	
Education				
Illiterate	37 (55.2)	38 (67.9)	75 (61.0)	
primary	20 (29.9)	14 (25.0)	34 (27.6)	
Metric	7 (10.4)	2 (3.6)	9 (7.3)	0.52
Inter	2 (3.0)	1 (1.8)	3 (2.4)	
Graduate	1(1.5)	1 (1.8)	2 (1.6)	
Occupation				
House wife	58 (86.6)	53 (94.6)	111 (90.2)	
Private job	3 (4.5)	1 (1.8)	4 (3.3)	0.40
Masi	1 (1.5)	1 (1.8)	2 (1.6)	
Farmer	5 (7.5)	1 (1.8)	6 (4.9)	
Family structure				
Joint family	36 (53.7)	31 (55.4)	67 (54.5)	0.86
Single	31 (46.2)	25 (44.6)	56 (45.5)	
Union council				
Hyderabad	27 (40.3)	18 (32.1)	45 (36.6)	
Nawabshah	18 (26.9)	22 (39.3)	40 (32.5)	0.336
Larkana	22 (32.8)	16 (28.6)	38 (30.9)	
Duration of marriage (Years)				
1-5	7 (10.4)	4 (7.1)	11 (8.9)	
6-10	27 (40.2)	28 (50)	55 (44.7)	0.465
11-15	20 (29.8)	18 (32.1)	38 (30.8)	
16-20	13 (19.4)	6 (10.7)	19 (15.4)	
Any person in home influences the women's uptake of, or decision-making				
Husband	36 (53.7%)	20 (35.7%)	56 (45.5%)	
Fathers in law	12 (17.9%)	15 (26.8%)	27 (22.0%)	
Mother in law	10 (14.9%)	15 (26.8%)	25 (20.3%)	0.03*
Both (Father & Mother in law)	4 (6.0%)	6 (10.7%)	10 (8.1%)	
Herself	5 (7.5%)	0	5 (4.1%)	

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

for its growth. This deficiency of micronutrients in mother risks the health and life of both, the mother and the fetus. Thus it is crucial to understand the role of antioxidant micronutrients

in influencing successful outcome of pregnancy and improving maternal health.

A study has been conducted in Sindh, a province of Pakistan to assess the role of antioxidant on maternal and fetus health mothers with a history of recurrent pregnancy loss were studied.

Table-II: Showing the maternal outcomes in the control and experimental group.

Maternal Outcome	Active drug n= 63 (%)	Placebo drug n=54 (%)	Total n=117 (%)	*p*-value (2-tail)
Maternal outcomes (including abortion, premature birth, still birth, and live birth)	23 (36.0)	8 (14.8)	31 (26.4)	0.008
Total			117	

Table-III: The rate of child and mother mortality in both groups.

Areas of improvement	Active arm	Placebo arm
Birth rate in women with RPL	28.3%	7.1%
Still births	1.2%	4.1%
Maternal mortality	2.1%	6.5%

PATIENTS AND METHODS

A Double Blind Randomized Control Trial (RCT) method was used. Mothers who had with a history of at least three abortions and frequently reported were randomly selected from tertiary care hospitals.

Antioxidants as well as Placebo tablets were especially prepared having same color, size, odor and packing. 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 experts.

The plan was recruited and registered the total 200 participants. (Hundred for control and 100 for experimental armed as arbitrary number in each arm in order to properly determine the outcome of RPL). Both types of sampling techniques purposive and snow ball were used after verbal screening for RPL at teaching tertiary care hospitals to identify the recurrent pregnancy losses mothers. Exclusion Criteria the following were excluded:

- Mother with a known medical cause of RPL
- Mothers with a chronic medical condition including Rubella, Syphilis, Diabetes, Hypertension, and Thyroid deficiency which may have a direct effect on the RPL.
- Mothers who has been exposed to Radiation or Toxins prior to the study.

During procedure neither the Principal Investigator (PI) nor staff of the health center knew about the drug regimens, as per the pre-requisite of a Double Blind Randomized control trial study. After the registration of the participant at the health center, the Women Medical Officer (WMO) and Lady Health Visitor (LHV) gave one drug box, which was already coded with a number randomly selected. The same code number was also written on the participant's pre-structured follow-up questionnaire. All the participants were completely informed about the trial procedure and were well aware of trial objectives and they would be required to report to the hospitals (LUMHS, SBBMU Larkana and PMC Benazirabad) every month and expected to take prescribed medicines; they were chosen for six months duration. The participants were asked to take one tablet daily after breakfast till the fetal conception developed. Furthermore, they were also advised to continue same tablets three months more after conception and report every month at the hospitals for routine medical check-ups until the child was born. They were strictly asked to avoid all other medications except for emergencies.

Data Analysis

Data were analyzed in SPSS version 21. Frequency and percentages were used to present the data. Chi-square test was applied for the comparsion of variables between groups. A *p*-value <0.05 was considered as a significant value.

RESULTS

The aim of research was to study chances of survival for the fetus of mothers with a history of spontaneous abortions. Out of total 123 selected cases which were identified in three tertiary care teaching hospitals. Sixty Seven (fig) of these mothers were part of the active arm which received the antioxidants while 56 were part of the experimental group which received placebo. There was no significant difference in demographics of both groups as the age, education; family structure except family influence was quite different in both groups as seen in (table-I) where *p*-value was statistically significant. In our study trial the rates of RPL were found 8.9% in mothers in the Placebo arm while in the active arm, the risk remained 14.9%.

In case of RPL, more than 50% of all the participants were between the ages of 26 and 30 while 20% of all these mothers were above the age of 21 years. The mean age of mothers in both arms, i.e. active and Placebo was 30 years (SD=3.59).

Most of the mothers 61% with a history of recurrent participants had more than 5 years of education while the percentage remained 25% in the placebo arm of all the mothers in study. Only 7% received education till matric while only 2% of these mothers had done their graduation, overall the mean years of education were higher for the active arm than placebo arm, i.e. 7.5 and 4.5 years respectively.

Employments of all nature were taken in to consideration for this category and it was found 13.4% of the mothers in active arm were employed while the number remained 5.3% in the placebo arm.

It was found that the mean duration for which the mothers in the active arm had been married was 11.3 years (SD=4.45) while the duration remained 10.6 years (SD=3.75) for the placebo arm. On average, it was found that 31% of all the participant in this study had been married for 11 to 15 years while 15.4% had been married for 16 to 20 years.

Being a male dominated society, in Pakistan the role of the decision maker is usually assumed by the eldest male of family considered to be the family head. All decisions are made by these heads of the family which may be anyone from the husband to the father-in-Law and in many cases, the mother-in-Law. In our study the decision maker in the family was husband in 46% of the cases while the father-in–law was head in 22% of all the cases. In the remaining cases, mother-law was consider to be the decision maker in 20% of the cases while mother themselves had such powers in only 4% of the cases.

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 as seen in table-II and fig.

A total of 10.4% of all mothers in the experimental group gave live births compared to the 3.5% in the controlled groups. The rate of premature births was also 10.4% for the experimental group while no such births were recorded in control group.

The results also revealed that antioxidants also improved the health of the mother along with the infant. Mothers in experimental group were more likely to survive compared to mothers that did not receive antioxidants this was just an incidental finding (table-III).

The results of the study confirm that antioxidants have a positive impact on RPL. Not only did women that received antioxidants have a better chance of conception, but also had a

higher chance of giving live birth compared to women who did not receive antioxidants as seen fig. These findings are consistent with previous studies which show that micronutrients and vitamins significantly improve the chances of live birth and thus can be used for women with a history of RPL to help them have a successful pregnancy outcome[9-11].

DISCUSSION

The aim of the study was to assess whether antioxidants can favorably affect the health of the mother and child and their survival. This was achieved by measuring the rate of RPL in mothers that received antioxidant supplements with mother who did not receive them. A study was conducted to investigate the association between maternal intakes of antioxidants including B-carotene, vitamin C and E, copper, and zinc. It was found that higher maternal dietary vitamin C intake was associated with the reduced risk of any allergic disease[12].

The women who were administered antioxidants in the studies showed improvement in the birth rate, chances of outcome, reduction in still birth, maternal mortality, and gestational duration. Antioxidants are powerful and there are few trials investigating antioxidant supplementation in female reproduction. However, before clinicians recommend antioxidants, randomized controlled trials with sufficient power are necessary to prove the efficacy of antioxidant supplementation in disorders of female reproduction. Serial measurement of oxidative stress biomarkers in longitudinal studies may help delineate the etiology of some of the disorders in female reproduction such as pre-eclampsia[13]. In our study we put mandatory blood test of total oxidative stress test, but due to lack of funding and electricity breakdown many samples were not analyzed due to blood hemolysis.

Although antioxidants such as folate, zinc, and thiols may help enhance fertility, the available data are contentious and must be evaluated in controlled studies with larger populations[14]. In our study we used vitamin C,E and Se but not in larger population still this need lot of funding and good trial protocol to reduce the RPL.

In one of study found that increased free radical activity has been implicated in the pathogenesis of recurrent abortion. Plasma ascorbic acid, α-tocopherol, total thiols, in 120 women with recurrent abortion. Recurrent aborters were divided into four subgroups according to the etiology: autoimmune (AUTO,

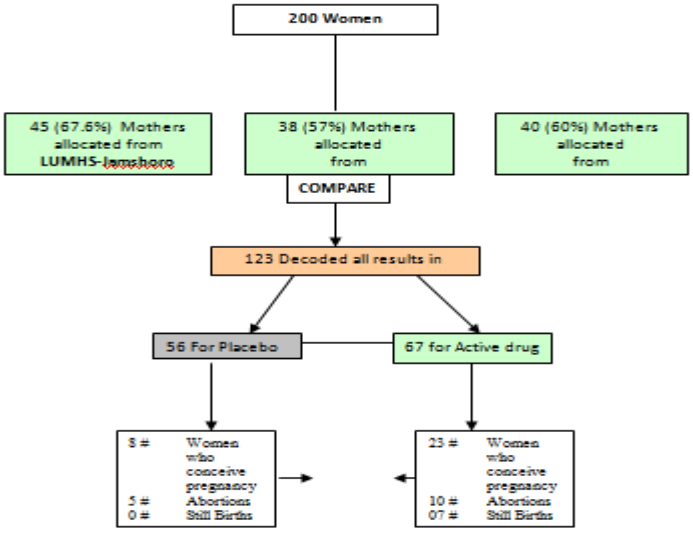

Figure: Results of allocated trial profile of study.

n=25), luteal phase defect (LPD, n=25), anatomical defect (AD, n=20) and unexplained (UNEx, n=50). Plasma levels of ascorbic acid, α-tocopherol, and erythrocyte GSH were significantly decreased in AUTO, UNEx and LPD subgroups than those in two control groups and the AD group (ANOVA). Also, the imbalance between antioxidant defense and free radical activity is more evident in the AUTO subgroup. As a conclusion, although impaired antioxidant defense may be responsible for recurrent abortions[15]. The decrease of those antioxidants may play a significant role in women with habitual abortion[16]. However, in our study I we tried to find by using vitamin C, E and Se but there was no statistical difference between the two arms except for those cases which were not conceived as the *p* value was calculated to be 0.003. It can be seen that the rate of abortion, still births, and live birth was high for the active arm as compared to the placebo arm. The chances of conception and trend of birth towards active arm showed that there may be some positive results in that side as compared to the placebo respectively, that mean some more intensive type of molecular or pathological research required in set-up in the future seeing the mechanism of Antioxidants.

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

The use of antioxidants before conception and during pregnancy significantly improves the chances of live births and outcome in general.

This essential and steered research trial if demonstrate positive results on the pregnancy result this might be offered to the bigger scale on national level through any pharmaceutical backing. We can recommend this on policy level in ANC for reducing the RPL after larger trial.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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