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The efficacy and safety of vitamin C administration to women with history of premature preterm rupture of membrane in prevention of such event in current pregnancy: Randomized controlled clinical trial

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ABSTRACT

Background: When rupture of membrane happens before onset of labor, the condition in obstetric practice is defined as "Prelabor rupture of membranes (PROM)" leading to leakage of amniotic fluid through ruptured chorioamniotic membranes and the conditions happens before 37 weeks of pregnancy the term "preterm PROM (PPROM)" is applied. Lack of vitamin C has been suggested as a predisposing factor and vitamin C supplementation has been suggested as a preventive measure.

Aim of the study: This study was aimed to determine the efficacy and safety of administration of vitamin C women with history of premature preterm rupture of membrane in prevention of such event in current pregnancy.

Patients and methods: The present randomized controlled clinical trial was performed in Maternity and Children Teaching Hospital in Al-Diwaniyah province in Iraq. It included 100 women with previous history of premature preborn rupture of membrane who were randomly allocated into two groups. The first group, the study group included 55 women who received vitamin C supplementation orally staring from 14 weeks gestation and the second group, the reference group was the placebo group (n = 45). Data regarding age, previous abortion, body mass index, number of previous pregnancies and previous abortions were obtained and outcome variables included gestational age at which rupture of membrane happened, gestational age at which delivery happened and birth weight were collected.

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Results: Vitamin C was able to significantly increase the GA at rupture or membrane (p = 0.033), form 29.00 ± 2.92 weeks to 30.11 ± 2.21 weeks. Vitamin C was also able to significantly increase the GA at birth (p = 0.019), form 32.04 ± 2.88 weeks to 33.31 ± 2.43 weeks. In addition, Vitamin C was also able to significantly increase the birth weight (p = 0.019) from 1951.10 ± 869.72 gram to 2409.10 ± 613.44 gram.
Conclusion: Vitamin C Administration to women with previous history of Premature Preterm Rupture of Membrane is efficient and safe in prevention of such event in current pregnancy.

Keywords: *Preterm premature rupture membrane, vitamin C, pregnancy, predisposing factors, Iraq*

INTRODUCTION

When rupture of membrane happens before onset of labor, the condition in obstetric practice is defined as "Prelabor rupture of membranes (PROM)" leading to leakage of amniotic fluid through ruptured chorioamniotic membranes and the conditions happens before 37 weeks of pregnancy the term "preterm PROM (PPROM)" is applied.[1–3] PROM is attributed to a variety of mechanisms. Basically, physiological weakening of membranes[4] combined with contractions of uterus[5] can interact to produce such an event. Infection that reaches intra-amniotic place is often associated with it.[6] A number of risk factors have been shown to be associated with increased risk of PPROM such as cigarette smoking,[7] use of illicit drug, poor socioeconomic status,[8] low weight, disorders of connective tissue,[9] overdistension of uterus, third of second trimester vaginal bleeding, cervical length that is short,[10] a history of PPROM and nutritional deficiencies of copper and ascorbic acid.[11–13] Nevertheless, in most cases, no clear cause can be blamed.[14]

A variety of factors play a role in accelerating weakening of membranes and eventual rupture.[15] For instance, local increment in cytokine levels,[15] lack of balance between metalloproteinases and their inhibitors, increased activity of proteases and collagenases[16] and other factors which may raise pressure inside uterus.[14]

It is among the most prevalent obstetrical issues, affecting 10–20% of all pregnancies. PPROM only affects 3% of pregnancies, yet it accounts for one-third of all preterm births and is associated with higher rates of neonatal and maternal morbidity and mortality.[17]

All aspects of the collagen metabolism (synthesis, secretion and degradation) are affected by vitamin C[18] so, decreased level of vitamin C particularly at 2nd trimester which led to decreased collagen synthesis and ultimately increase the prevalence of PPROM.[19] Additionally, vitamin C level during gestation used as a diagnostic tool to PPROM.[20] Other studies revealed that the pregnant women with PPROM are associated with lower serum levels of vitamin C compared to the control group.[21] The correlation between consumption of vitamin C and occurrence of PPROM is still controversial. Therefore, the current study focused to determine the vitamin C function prevent occurrence of PPROM.[17]

The current study was aimed to determine the efficacy and safety of vitamin C administration in prevent occurrence of PPROM in female during the gestation.

PATIENTS AND METHODS

The present randomized controlled clinical trial was performed in Maternity and Children Teaching Hospital in Al-Diwaniyah province in Iraq. One hundred women participated with previous history of premature preborn rupture of membrane and arbitrarily allocated into two groups. One of the groups included 55 women who received

vitamin C supplementation orally staring from 14 weeks gestation and the other group, the reference group was the placebo group (n = 45). Data regarding age, previous abortion, body mass index, number of previous pregnancies and previous abortions were obtained and outcome variables included gestational age at which rupture of membrane happened, gestational age at which delivery happened and birth weight were collected.

The present study was authorized by the College of Medicine, University of Al-Qadisiyah Ethical Committee and verbal consent was obtained from every participant. Statistical analysis was performed using statistical package for social sciences (SPSS) software and Microsoft Office Excel program. Numeric data were presented as range, standard deviation, inter-quartile range, mean and median; whereas, qualitative data were expressed and number and percentage. Independent sample t-test was used to compare means, Mann Whitney U test was used to compare medians and chi-square test was used to compare frequencies. The level of significance was considered at $p \leq 0.05$.

RESULTS

Comparison of demographic characteristics and obstetric history events between group of vitamin C and group of placebos as revealed in Table 1. The results showed insignificant difference in age between vitamin C group and placebo group, 25.65 ± 5.17 years versus 24.29 ± 4.98 years (p = 0.0185). the results also showed insignificant difference BMI between vitamin C group and placebo group, 25.96 ± 3.94 kg/m^2 versus 25.16 ± 3.42 kg/m^2 (p = 0.0185). The results also demonstrated insignificant difference in the women of previous pregnancies and occurrence of abortions between vitamin C group and placebo group ($p > 0.05$).

Comparison of outcome characteristics between vitamin C group and placebo groups is shown in Table 2. Vitamin C was able to significantly increase the GA at rupture or membrane (p = 0.033), form 29.00 ± 2.92 weeks to 30.11 ± 2.21 weeks. Vitamin C was also able to significantly increase the GA at birth (p = 0.019), form 32.04 ± 2.88 weeks to 33.31 ± 2.43 weeks. In addition, Vitamin C was also able to significantly increase the birth weight (p = 0.019) from 1951.10 ± 869.72 gram to 2409.10 ± 613.44 gram.

DISCUSSION

The results exhibited 35% of prematurely babies have PROM. All PROM history patients are significantly more likely to experience it again in subsequent pregnancies.[22] Woods et al. in 2001[23,24] revealed that the oxidative stress and formation of reactive oxygen species is the major reason for pathological mechanism leading to PROM. They proposed that collagenolytic enzymes might be activated and fetal membrane integrity compromised by reactive oxygen species, which are produced by the body in response to a variety of stressors, including infections, smoking, bleeding, and cocaine use. They also supposed that a lipid-soluble antioxidant (vitamin E), act as a free radical scavenger and inhibit the lipid peroxidation and damaging of the cell membrane, while a water-soluble antioxidant (vitamin C), promotes collagen synthesis while recycling vitamin E.[25]

The current study determined the effect of VC administration on PPROM women to observe the efficacy and safety to prevent such complications and promised to lengthen the gestational age at which membrane rupture as well as lengthen the duration of pregnancy till delivery and improve birth weight. In the study done by Ghomian et al in 2013[12] on 170 PPROM women during pregnancy, who were randomly allocated into two groups a study group receiving vitamin C and a reference group, the authors concluded that "Vitamin C supplementations after 14th weeks of gestation can prevent from PPROM in women with the history of PPROM" and this finding is supportive to our results.

Preterm delivery and its associated maternal and fetal morbidity and mortality have been shown

TABLE 1. Comparison of demographic characteristics and obstetric history events between vitamin C group and placebo group.

Characteristic	Total *n* = 100	VC group *n* = 55	Placebo group *n* = 45	*p*
Age (years)				
Mean ± SD	25.04 ± 5.11	25.65 ± 5.17	24.29 ± 4.98	0.185 I NS
Range	17–40	18–40	17–38	
BMI(kg/m^2)				
Mean ± SD	25.60 ± 3.72	25.96 ± 3.94	25.16 ± 3.42	0.282 I NS
Range	17–34	17–34	19–32	
Number of pregnancies				
Median (IQR)	2 (2)	2 (2)	2 (2)	0.418 M NS
Range	0–7	0–6	0–7	
Previous abortions				
Positive, *n* (%)	23 (23.0%)	15 (27.3%)	8 (17.8%)	0.262 C NS
Negative, *n* (%)	77 (77.0%)	40 (72.7%)	37 (82.2%)	

n: number of cases; SD: standard deviation; BMI: body mass index; IQR: inter-quartile range; I: independent samples t-test; M: Mann Whitney U test; C: chi-square test; NS: not significant.

TABLE 2. Comparison of outcome characteristics between vitamin C group and placebo groups.

Characteristic	Total *n* = 100	VC group *n* = 55	Placebo group *n* = 45	*p*
GA at rupture or membrane (weeks)				
Mean ± SD	29.61 ± 2.60	30.11 ± 2.21	29.00 ± 2.92	0.033 I*
Range	23–35	23–35	24–35	
GA at birth (weeks)				
Mean ± SD	32.74 ± 2.70	33.31 ± 2.43	32.04 ± 2.88	0.019 I*
Range	27–37	29–37	27–37	
Birth weight (weeks)				
Mean ± SD	2203.00 ± 770.64	2409.10 ± 613.44	1951.10 ± 869.72	0.003 I**
Range	700–3400	1000–3400	700–3400	

*n: number of cases; SD: standard deviation; GA: gestational age; I: independent samples t-test; *Significant at p ≤ 0.05; **Significant at p ≤ 0.01.*

to be significantly connected to PPROM.[21,26] One of the main blamed mechanisms is metabolism of collagen, nevertheless, the list of causes is long.[12] Therefore, it has been postulated that using vitamin C in pregnancy may lead to strengthening of amniochorion membranes and thereby leading to reduction of incidence of PPROM.[12] It has been shown that women with PPROM have relatively low level of vitamin C[27] justifying vitamin C supplementation during pregnancy aiming at reducing the rate of such complication.

Our results are also in accordance with that reported by Barret et al.[28] who concluded that "the administration of 100 mg of vitamin C in pregnant women after 20th weeks of gestation can significantly decrease the incidence of PROM

and PPROM." Other authors have found similar results.[29]

2064 cohort study of expectant women with singleton gestations was investigated by Siega-Riz et al.[30] Preterm birth due to premature membrane rupture was twice as likely to occur in women with preconception total vitamin C intakes below the 10th percentile (relative risk: 2.2; 95% CI: 1.1, 4.5). For second-trimester ingestion, this risk was slightly reduced (relative risk: 1.7; 95% CI: 0.8, 3.5). Women who consumed little vitamin C during both time periods were most at risk of preterm premature rupture of the membranes. Vitamin supplementation may be an effective interventional therapy, they said.

At 20 weeks of gestation, 109 individuals were randomly randomized to receive either a placebo or 100 mg of vitamin C, according to Casanueva et al.[20] The levels of plasma vitamin C in both groups significantly decreased during the pregnancy, with no apparent variations between the groups. PROM prevalence 24.5% in the placebo group while 7.69% in the group administered with vitamin C despite the low dose of administration (relative risk: 0.26; 95% CI: 0.078, 0.837). The scientists came to the conclusion that vitamin C successfully lowers the incidence of PROM after 20 weeks of gestation.

CONCLUSION

Administration of Vitamin C via women with PROM history is efficient and safe in Prevention of Such Event in Current Pregnancy.

ETHICAL APPROVAL

The current study was permitted by the Ethical Committee approval of College of Medicine, University of Al-Qadisiyah.

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CONFLICT OF INTEREST

No conflict of interest was declared by the author.

INFORMED CONSENT

Verbal consent was obtained from every participant.

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