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Review Article

Is vitamin C able to prevent premature rupture of membranes?

Citra Aryanti*

Department of Obstetrics and Gynecology, Muhammadiyah Hospital, Medan, Indonesia

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***Correspondence:**
Dr. Citra Aryanti,
E-mail: citra.aryanti@hotmail.com

ABSTRACT

Premature rupture of membranes (PROM) is leakage of amniotic fluid through ruptured chorioamniotic membranes that occur before starting the labor pain at any gestational age. This is one of the most common problems in obstetrics with many adverse pregnancy outcomes. Main and final mechanisms of membrane rupture is disturbances in its collagen content metabolism. Vitamin C is found to stabilize the cross link triple helix collagen structure and scavange oxidant that involved in PPROM. Association between vitamin C and PROM remained controversial because studies show variaty results. It is important to know the effective dose of vitamin C because giving large doses of vitamin C can cause adverse reactions.

Keywords: Premature rupture of membranes, Amniotic membrane, Vitamin C, Collagen, Doses

INTRODUCTION

Premature rupture of membranes (PROM) is leakage of amniotic fluid through ruptured chorioamniotic membranes that occur before starting the labor pain at any gestational age.[1] This is one of the most common problems in obstetrics and affects 10-20% of all pregnancies.[2] PROM cause adverse pregnancy outcomes such as preterm delivery and high rates of maternal morbidity and and accounts for 70% perinatal mortality worldwide.[3,4] So that, this case is critically important to be evaluated in impact of clinical and public health problem.[5]

Main and final mechanisms of membrane rupture is disturbances in collagen metabolism because it is develops amniotic membrane's mechanical integrity and stress tolerance.[5] Vitamin C is involved in maintenance of collagen synthesis, collagen secretion, collagenolysis, and antioxidant that blocks the damaging effects of oxidative stress in vitro.[7]

Variations in the studies led to controversial debate in using or not using vitamin C as supplementation to prevent PROM.[8] Preterm born babies' care is especially challenging by lack of facilities and considered as high cost. Hence it becomes imperative to carry out review about relationship between vitamin C and PROM.

Premature rupture of membranes (PROM)

Premature rupture of membranes (PROM) is defined as a leakage of amniotic fluid becuase chorioamniotic membranes ruptured that occurs before the onset of labor in pregnancies of at least 20 weeks. This is one of the most common problems in obstetrics and affects 10-20% of all pregnancies[2] with high rates of maternal and perinatal morbidity and mortality.[3,4]

Similar to its vast incidents, the pathophysiology is complex and multifactorial.[8] One of the main role is the failure integrity of chorioamniotic membrane (Fig. 1). It has been reported that prematurely ruptured membranes have less collagen content and hence less tension resistance.[9] The compact layer of stromal matrix forms the main fibrous integrity of the amniotic membrane. The collagen contents are secreted by mesenchymal cells in the fibroblast layer. Interstitial collagens (types I and III) predominate and form parallel bundles that maintain the mechanical integrity of amniotic membrane. Collagens

type V and VI form filamentous connections between interstitial collagens and the epithelial basement membrane.[10]

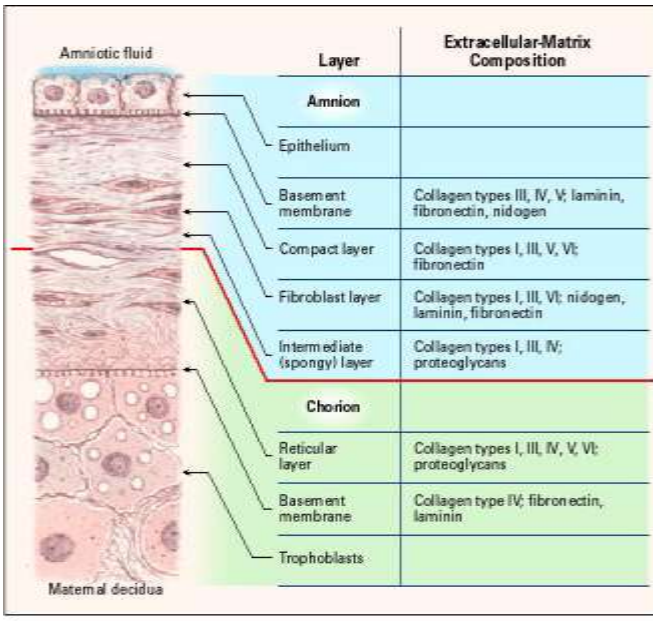

Figure 1: Schematic presentation of the structure of the foetal membrane at term. The Extracellular matrix components of each layer are shown.

Vitamin C

Vitamin C is a white crystalline sugar nutrients that are essentially required by the body for its various biochemical and physiological processes that is not synthesized by human body. Backbone of vitamin C is L-ascorbic acid, a dybasic acid with an enediol group slong with five heterocyclic lactone rings. It is an unstable, easily oxidized acid and can be destroyed by oxygen, alkali and high temperature.[11] The structure of dehydroascorbic acid, the first oxidation product of ascorbic acid (Figure 2), has been analyzed by x-ray crystallography to be a dimer. Electrochemical studies have indicated that ascorbic acid and dehydroascorbic acid form a reversible redox couple.[12]

Dietary requirement of vitamin C

The controversy about vitamin C requirements continues to this day. There has been much discussion concerning the safety of large doses of vitamin C that needs to be consumed for optimum well-being. The current recommended dietary daily allowances for vitamin C are 90 mg for men and 75 mg for women. Ascorbate begins to appear in the urine from the intakes of 60 mg/d. Intakes of 250 mg/d and higher are required to saturate ascorbate concentrations in plasma and white blood cells.In recent study, vitamin C supplementation is considered relatively safe, even in megadose levels 1-4 g/d.[13]

Absorption and metabolism of vitamin C

In human and guinea pigs, the absorption of vitamin C occurs in the buccal mucosa, stomach and the small intestine through passive diffusion and active transport system. Body ascorbate reaches a maximum of 20 mg/kg body weight, i.e. with a total pool size of about 1.5 g, when ascorbate intake is increased from 30 to 180 mg/day. Above this level of intake, the excretion in the urine rises rapidly. Since the absorption mechanism in the gut and kidney can reach a saturation point, it is better to take multiple and smaller doses of vitamin C through out the day than one large dose. Ascorbic acid can be found naturally in chemical forms of L-xylo-ascorbic acid and D-xylo-ascorbate. It is reversibly oxidized to L-dehydroascorbic acid on exposure to copper, heat or mildly alkaline conditions. Both L-ascorbic acid and L-dehydroascorbic acid are physiologically active forms of vitamin C. The principal pathway of oxidation is believed to involve the removal of two electrons that yield first the ascorbate free radical and then dehydroascorbate. These molecules react together to form one molecule of ascorbate and one of dehydroascorbate. Alternatively, ascorbate free radical may be reduced by a microsomal NADH-dependant enzyme, mono-dehydro-L-ascorbate oxidoreductase to ascorbate.[11]

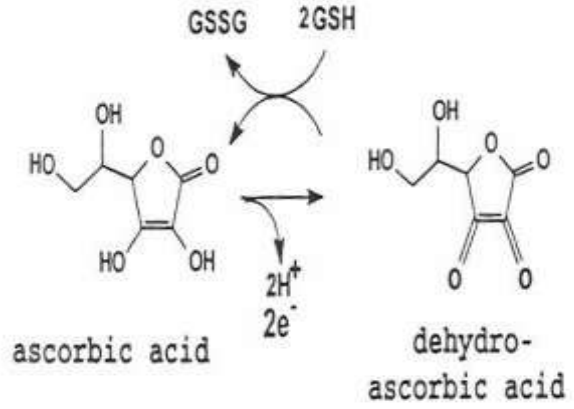

Figure 2: Ascorbic acid and dehydroascorbic acid. Ascorbic acid is the reduced form of vitamin C. The oxidized form, dehydroascorbic acid, can be reduced back to ascorbic acid by glutathione (GSH).

Vitamin C and PROM

Distrubance of collagen,[14] as the main component of the amniotic membrane's extracellular matrix, is considered as the main factor in premature rupture of membranes.[15] Kanayama et al showed that patients with PROM had low collagen content[16] with emphasization of in vitro study by Plessinger et al that showed excessive damage to invitro amniotic epithelium from exposure to hypochlorous acid.[17] But, other studies have reported no differences in collagen content between membranes that have ruptured prelabor and those that have undergone timely rupture.[18]

Vitamin C is involved in maintenance of collagen and antioxidant.[7] Adequate level of vitamin C directly act to increased triple helix collagen mRNA posttransciption. In addition, it acts as an enzymatic cofactor to lysyl hydroxylase and prolyl hydroxylase to form hydroxyproline and hydroxylysine which provides triple helix stabilization.[8] Vice versa, inadequacy of vitamin C will increase 72-kDa type IV collagenase and metalloproteinases .[19] As an antioxidant, vitamin C acts as a reducing agent by delivering a hydrogen atom with its single electron to stabilizes single unpaired electron in the outer ring of reactive oxygen species.[20] Therefore, vitamin C plays role in maintaining mechanical and biomechanical strength of the chorioamniotic membranes structure and formation throughout gestation.[1]

In 1964, a relationship between maternal vitamin C status and the occurrence of PROM was first proposed that vitamin C plays an essential role in the synthesis of collagen as well as its stabilization by cross-linking.[21] Hadley et al. (1990) have shown that there were lower levels of ascorbic acid (vitamin C) in serum, leucocytes, and amniotic fluid of cases with PPROM as compared to the control group yet it was unsure considering the effect of hemodilution.[22] Matthews et al. (2005) showed vitamin C concentration decline as incresing gestational age due to physiologic hemodilution, reduce intake, and increased oxidative stress during pregnancy.[23] Then, Casanueva et al. (2005) stated that the leukocyte ascorbate concentration >18 ìg/10^8 cell determined to protect against PROM.[24]

Association between vitamin C and PROM remained controversial because studies show variaty results.[8] The different results from the studies may be due to the different population, methods, and assays that were being used. Reference values for vitamin C seems to be influenced by the assay method and study design, albeit the widely accepted reference value for normal of fasting samples is 26.1-84.6mmol/l (>0.6 mg/dl, > 20mg/10^8cells, >114 nmol/10^8 cells), while for deficiency state is a value of < 11mmol/l (<0.2mg/dl, <10 mg/10^8 cells, <57 nmol/10^8 cells).[25]

Borna et al. (2004) in addition found a significant increase in latency period for those that had Vitamin C and E supplementation after PROM.[26] Hajifoghahaet et al. (2005) also showed administration of 100 mg of vitamin C in pregnant women after 20 weeks of gestation can significantly decrease the incidence of PROM and PPROM.[27] Ghomian et al. showed similar result that PPROM and PROM were significantly decreased significantly in the group that received 100 mg vitamin C from 14 weeks of gestational age compred to control (31.8% vs 44.7%; $p<0.05$ and 18.8% vs 34.4%; $p<0.05$).[28] Casanueva et al. (2005) showed that 100 mg of Vitamin C per day was sufficient to maintain leukocyte ascorbic acid concentration at a level above 18 mg/10^8 cells, level to protect aginst PROM.[24] In addition, Simhan et al. (2005) reported vitamin C usage significantly increased the gestational age at delivery, neonatal Apgar score, birth-weight, and latency period.[29] Siega et al. (2003) emphasized by showing groups with vitamin C intake of less than 10^{th} percentile had twice the risk of preterm delivery because of PROM.[1]

Contrary to that, Vermilion et al. (2000) showed no difference incidence of PROM between group that received vitamin C plus ferrous sulfate compared to the control group.[30] Steyn et al. (2003) stated that vitamin C supplementation may only be apparent in the patient with a history of vitamin C deficiency.[30] Even in Spinnato et al. (2008) study, it has been showed that too much vitamin C caused an increase in the incidence of PROM.[32] Author said that it was crucial to determine vitamin C dosage that need to prevent PROM because high levels can cause contrary function.[20]

CONCLUSIONS

Supplementation of vitamin C of 100 mg was showed to effectively decreased incidence of premature rupture of membrane. Giving large doses of vitamin C can cause adverse reactions. Yet, since drug metabolism varies among people, authors need to carry out studies in each population setting for developing a comprehensive guideline to the community.

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