

The Relation between Serum Ascorbic Acid Concentration and Preterm Premature Rupture of Membranes

Thesis

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Presented by

Karim Mohamed Ezz El Din Mohamed

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Ain Shams University

Obstetric and Gynecology Resident at Manshyet El Bakry Hospital

Under supervision of

Prof. Sherif Mohamed Habib

*Professor of Obstetric and Gynecology
Faculty of Medicine - Ain Shams University*

Dr. Mohamed Hussein Mostafa

*Assistant Professor of Obstetric and Gynecology
Faculty of Medicine - Ain Shams University*

**Faculty of Medicine
Ain Shams University**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبَّحَانَكَ لَا يَلْمُ لَنَا
إِلَّا مَا عَلِمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
<i>AF</i>	<i>Amniotic fluid.</i>
<i>AFI</i>	<i>Amniotic fluid index</i>
<i>AFS</i>	<i>Amniotic fluid-derived stem</i>
<i>BV</i>	<i>Bacterial vaginosis</i>
<i>CAPs</i>	<i>Contraction-associated proteins</i>
<i>CRH</i>	<i>Corticotropin-releasing hormone</i>
<i>CRP</i>	<i>C-reactive protein</i>
<i>CS</i>	<i>Caeserean section</i>
<i>CSF</i>	<i>Cerebrospinal fluid</i>
<i>DAO</i>	<i>Diamine oxidase.</i>
<i>DHEA-S</i>	<i>Dehydroepiandrosterone sulfate</i>
<i>ELISA</i>	<i>Enzyme-linked immune sorbent assay.</i>
<i>FFN</i>	<i>Fetal Fibronectin</i>
<i>GA</i>	<i>Gestational age</i>
<i>HCG</i>	<i>Human chorionic gonadotrophins</i>
<i>HS</i>	<i>Highly Significant</i>
<i>IL</i>	<i>Interleukin</i>
<i>LEEP</i>	<i>Loop Electrosurgical Excision Procedure</i>
<i>LPS</i>	<i>Lipopolysaccharide</i>
<i>MMPs</i>	<i>Matrix metalloproteinases</i>
<i>mRNA</i>	<i>Messenger Ribonucleic Acid</i>
<i>NS</i>	<i>Non significant</i>
<i>PG</i>	<i>Prostaglandin.</i>
<i>PPROM</i>	<i>Premature rupture of membrane.</i>
<i>PROM</i>	<i>Preterm premature rupture of membranes.</i>
<i>RDS</i>	<i>Respiratory distress syndrome.</i>
<i>S</i>	<i>Significant</i>
<i>TIMPs</i>	<i>Tissue inhibitors of matrix metalloproteinases</i>
<i>TLC</i>	<i>Total leucocytic count</i>
<i>TNF</i>	<i>Tumor necrotic factor</i>
<i>U/S</i>	<i>Ultrasonograph</i>

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) is defined as rupture of the chorioamniotic membranes before the onset of labor prior to 37 weeks of gestation. PPRM is further classified by gestational age: midtrimester (less than 24 weeks), early (24 to 34 weeks), and near-term (34 to 37 weeks) (*Mackeen et al., 2014*). Preterm premature rupture of the fetal membranes (PPROM) affects 2–4.5% of all pregnancies and is associated with perinatal morbidity and mortality (*Van De Laar et al., 2009*).

Preterm premature rupture of membranes is the leading known cause of preterm birth affecting approximately one-third of all births delivered prior to 37 weeks gestation (*Dadvand et al., 2014*). One of the primary causes of perinatal morbidity is intrauterine infection, which complicates 40–70% of PPRM cases (*Tita & Andrews, 2010*).

There are many known or suspected causal pathways to preterm premature rupture of membranes as black race, lower socioeconomic status, smokers, past history of sexually transmitted infections, previous preterm delivery, polyhydramnios and multiple pregnancy (*Simmons et al., 2010*).

Others are procedures such as cerclage and amniocentesis. The aetiology is multifactorial (*Medina & Hill, 2006*).

A significant association between low Vitamin C levels and premature rupture of membranes was found. It is thought that the mechanism for PPRM may be a degradation in the collagen of the amniotic sac, higher levels of ascorbic acid seem to be a protective factor against a weakened membrane leading to PPRM (*Osaikhuwuomwan et al., 2011*).

The micronutrient vitamin C is an effective water soluble antioxidant that scavenges several reactive oxygen species, thus reducing oxidative stress. It also acts as an enzymatic cofactor to the enzymes lysyl hydroxylase and prolyl hydroxylase, which is required for synthesis of hydroxyproline and hydroxylysine. Collagen requires hydroxyproline bridges across the triple helix to provide stability to it, Ascorbic acid also causes downregulation of the metalloproteinase-2 and biosynthesis of collagen where it is required for the formation of triple helical structure of collagen. Thus, ascorbic acid participates in the equilibrium between synthesis and degradation of collagen and this may be critical in reducing the occurrence of preterm PROM (*Shen et al., 2008*).

Vitamin C cannot be synthesized by the body hence it is only gotten from dietary sources or supplementation (*Steyn et al., 2003*). Dietary or supplemental dose of 60-100mg of Vitamin C has been recommended to maintain normal plasma levels (*Salminen & Alfthan, 2008*).

Studies propose a relationship between low vitamin C intake and an increased risk of preterm premature rupture of membranes. Also they propose that vitamin C can prevent premature rupture of membranes through its role as an antioxidant or in collagen synthesis and maintenance. Therefore, Vitamin C supplement is recommended to be administered for pregnant women with the history of PPRM during pregnancy to prevent PPRM (*Ghomian et al., 2013*).

AIM OF THE WORK

Research Hypothesis:

In women with Preterm premature rupture of membranes (PPROM), vitamin C may have a role in this condition.

Research Question:

In women with Preterm premature rupture of membranes (PPROM), is there a relation between serum vitamin C levels and this condition?

Aim:

This study aims to investigate the association between maternal serum vitamin C levels and occurrence of Preterm premature rupture of membranes (PPROM) in pregnant women.

Chapter 1

THE FETAL MEMBRANES

Fetal membranes are composed of two layers: an outer layer (chorion), an inner layer (amniotic membrane) (*Mamede et al., 2012*).

Inspection of the fetal membranes following delivery reveals amnion that is mildly adherent to the fetal side of the chorion. Small amounts of maternal decidual tissue can be observed attached to the outer, maternal side of the chorion (*Guller, 2011*).

Anatomy of the fetal membranes:

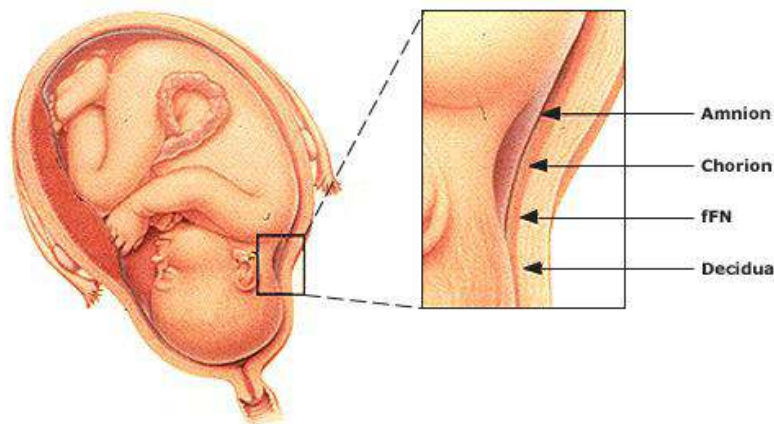


Figure (1): Fetal membranes: Anatomy (*Guller, 2011*).
(1) Amnion, (2) Chorion, (3) Fetal Fibronectin, (4) Decidua

Anatomy of the amnion:

Amnion is the thin membrane on the inner side of the placenta; it completely surrounds the embryo/fetus and delimits the amniotic cavity, which is filled by amniotic fluid (*Mamede et al., 2012*).

The fetal surface is smooth and glistening. Through amnion three umbilical vessels can be seen embedded in Wharton jelly, these are two umbilical arteries and one umbilical vein. The amnion is loosely attached to Wharton jelly except at the site of insertion of the umbilical cord in the placenta. The amnion contains no blood vessels or nerves, the nutrients it requires are supplied by the amniotic fluid (*McParland & Bell, 2004*).

Amnion is divided into 3 parts:

- Reflected amnion is fused to the chorion leavea.
- Placental amnion covers the placental surface and is in contact with the adventitial surface of chorionic vessels.
- Umbilical amnion covers the umbilical cord.

(Cunningham et al., 2010a)

Anatomy of the chorion:

The chorion is the outer fetal envelope which is adjacent to the outer aspect of the amnion, and through which the major branching umbilical vessels travel on the surface of the placenta. The chorion laeve is generally more nearly translucent than the amnion and rarely exceeds 1 mm thickness (*Cunningham et al., 2010a*).

Histology of the fetal membranes:

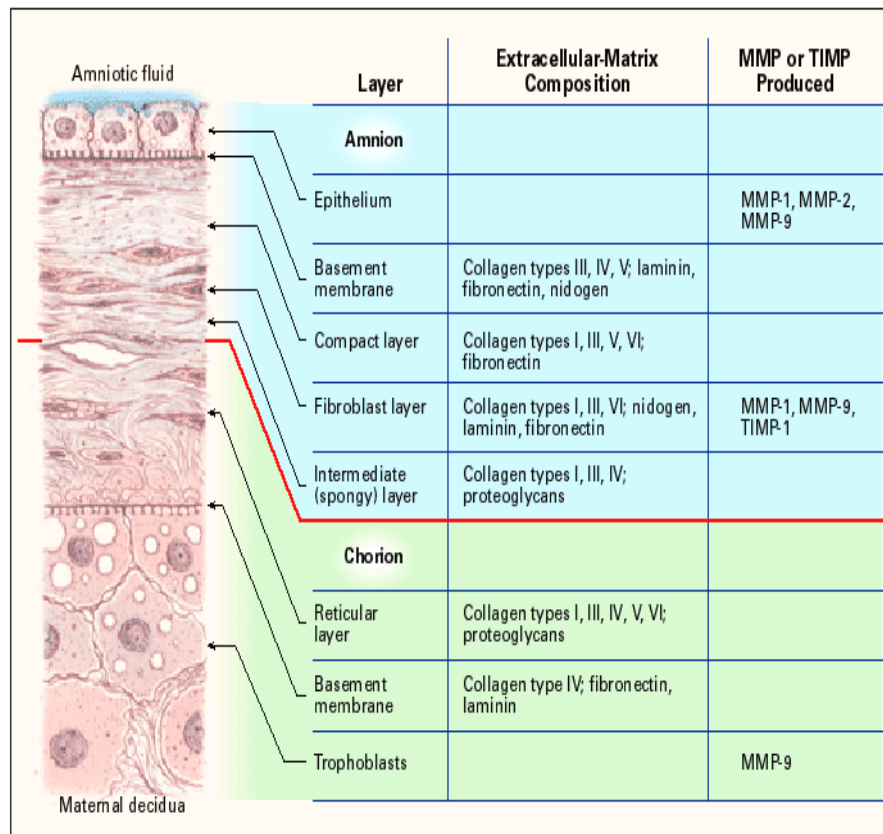


Figure (2): Schematic Representation of the Structure of the Fetal Membranes at Term. The extracellular-matrix composition of each layer and the production sites of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) are shown (*Parry and Strauss, 1998*).

Histology of the amnion:

According to *Mcparland & Bell (2004)*, the amnion consists of five layers which are from within outward:

a- The epithelium:

This is composed of a single layer of apparently simple non ciliated cuboidal cells.

b- The basement membrane:

This is a narrow band of thin layer of reticular tissue lying along the base of epithelial cells to which it is adherent securely.

c- The compact layer:

This is a relatively dense acellular layer of collagen fibers lying deep to basement membrane to which it is densely adherent and from which it cannot be separated.

d- The fibroblast layer:

It is the most complex of the five amniotic layers. It is composed of fibroblast network set in a mesh of reticulin. The only cells normally present are fibroblasts and Hofbauer cells (Macrophages). Normally, this layer forms a considerable part of the thickness of the amnion.

e- The spongy layer:

It is composed of extraembryonic celomicreticulum, contains a nonfibrillar meshwork of mostly type III collagen.