Reliability of Lactate Concentration in Vaginal Fluid in Prediction of PPROM

Thesis

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ABSTRACT

Lactate concentration is reported to be high in amniotic fluid (AF). Preterm prelabour rupture of membranes (PPROM) is defined as rupture of the fetal membranes prior to onset of labour in patients who has gestational age of less than 37 weeks. It occurs in about 3-5% of all pregnancies. The condition is associated with fetal and maternal complications, and might be a marker of imminent delivery, therefore among women with suspected (PPROM); it is of a great importance to accurately confirm the diagnosis.

In this study we try to assess whether lactate determination in vaginal fluid could be used as a diagnostic test for PPROM.

A lactate concentration > 4.4 mmol/L was found to be the best cut-off value for a positive "lac-test" and show a sensitivity of 96.3% and specificity 84.8%.

This thesis show the usefulness of determination of lactate in AF, which can be used in prediction of PPROM.

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List of Abbreviations

AF	*Amniotic fluid*
AFI	*Amniotic fluid index*
ANC	*Antenatal care*
BV	*Bacterial vaginosis*
CAPs	*Contraction-associated proteins*
CNS	*Central nervous system*
CRH	*Corticotrophin-releasing hormone*
CSF	*Cerebrospinal fluid*
DAO	*Diamine oxidase*
DHEA	*Dehydroepiandrosterone sulfate*
EFW	*Expected fetal weight*
FDA	*Food and drug administration*
FFN	*Fetal fibronectin*
GA	*Gestational age*
GBS	*Group B-streptococcus*
hCG	*Human chorionic gonadotropin*
IGFBP-1	*Insulin like growth factor binding protein-1*
LEEP	*Loop electrosurgical excision procedure*
LLETz	*Large loop excision of the transformation zone*
LOD	*Lactate oxidase*

LOD-PAP	*Lactic xoidase P-aminophenazone*
MMP	*Matrix metalloproteinases*
NSE	*Neuron specific enolase*
PAMG-1	*Placental alpha microglobulin-1*
PBEF	*Pre-B-cell colony enhancing factor*
PPROM	*Preterm prelabor rupture of membranes*
RDS	*Respiratory distress syndrome*
ROC curve	*Receiver operating characteristic curve*
ROM	*Rupture of membranes*
STD(s)	*Sexual transmitted diseases*
TIMP	*Tissue inhibitor metabolloproteinases*

First thanks to **ALLAH** *to whom I relate any success in achieving any work in my life.*

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INTRODUCTION

Preterm prelabour rupture of membranes (PPROM) is defined as 'rupture of the fetal membranes prior to onset of labour in a patient who has a gestational age of less than 37 weeks'. It occurs in approximately 3-5% of all pregnancies and accounts for one-third of all preterm births ***(ACOG, 2007)***. Also it is associated with risks of preterm delivery and with substantially increase risks of perinatal morbidity and mortality ***(Aagaard et al., 2005)***. This condition may be associated with fetal and maternal infections, cord complications and may be a marker of imminent delivery ***(Mercer et al., 2003)***.

The diagnosis of ruptured membranes is easy when there is an obvious leakage of amniotic fluid but more difficult when the leak is scanty or intermittent. The diagnosis of PPROM has relied on a combination of factors, including the women's history, pooling of amniotic fluid in the vagina at sterile speculum examination, microscopic examination of vaginal fluid and/or biochemical tests ***(Gaucherand et al., 1995)***.

The absence of a 'gold standard' for the diagnosis of PPROM has stimulated many researchers to search for a

clinically applicable marker of PPROM ***(Wiberg-Itzel et al., 2009).***

The lactate concentration is reported to be four to six times higher in AF than in fetal and maternal blood ***(Liu et al., 1999)***. The source of lactate in AF is the fetus, mainly through urine and lung excretion ***(Brace, 1997).*** Also it has been suggested the myometrium as another possible lactate producer ***(Quenby et al., 2004)***.

A positive "LAC test", that is a lactate concentration $\geq$ 4.5 mmol/l in vaginal fluid is reliable test for the diagnosis of rupture of membranes in pregnancies of 34 weeks of gestation or more ***(Wiberg-Itzel et al., 2005)***. It has been found a significant association between a positive LAC test and spontaneous onset of labour within 48 hrs in late gestations that is $\geq$ 34 weeks ***(Wiberg-Itzel et al., 2006)***.

AIM OF THE WORK

The aim of the study is to detect lactate in vaginal fluid and measure its concentration in a trial to evaluate the reliability of lactate concentration to diagnose suspected cases of PPROM.

THE FETAL MEMBRANES

The fetal membranes are composed of two layers: the amnion (inner layer) and the chorion (outer layer) **(Guller et al., 2010).**

Anatomy of the fetal membranes:

Anatomy of the amnion:

The amnion is a thin translucent membrane that contains the amniotic fluid and the fetus. 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 where they are firmly attached. The amnion contains no blood vessels or nerves, the nutrients it requires are supplied by the amniotic fluid **(McParland and Bell, 2004).**

It is divided into 3 parts:

1- Placental amnion: covers the inner aspect of the placenta.
2- Dependent amnion: 1-2 cm overlying the internal os of the cervix.
3- Reflected amnion: the reminder part of the amnion.

(Sagol et al., 2001)

Anatomy of the chorion:

The chorion is the specialized 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., 2010).**

Development of the fetal membranes:

Development of the amnion:

The amnion develops from an ectodermal cell nest in the dorsal aspect of the embryo 8 days after conception **(Calvin and Oyen, 2007).**

The amniotic cavity lies between the amnion and the ectodermal disc, it increases in size progressively. By the 3rd month, the amnion comes in contact with the chorion by closing the extra-embryonic coelom. It extends from the fetal surface of the placenta above to the internal os below and wraps the umbilical cord **(Ayad, 2002).**

Early in development the amnion is in contact with the body of the embryo, but about the fourth or fifth week fluid (liquor amnii) begins to accumulate within it. This fluid increases in quantity and causes the amnion to expand and ultimately to adhere to the inner surface of the chorion,

so that the extra-embryonic part of the celom is obliterated **(Cunningham et al., 2010).**

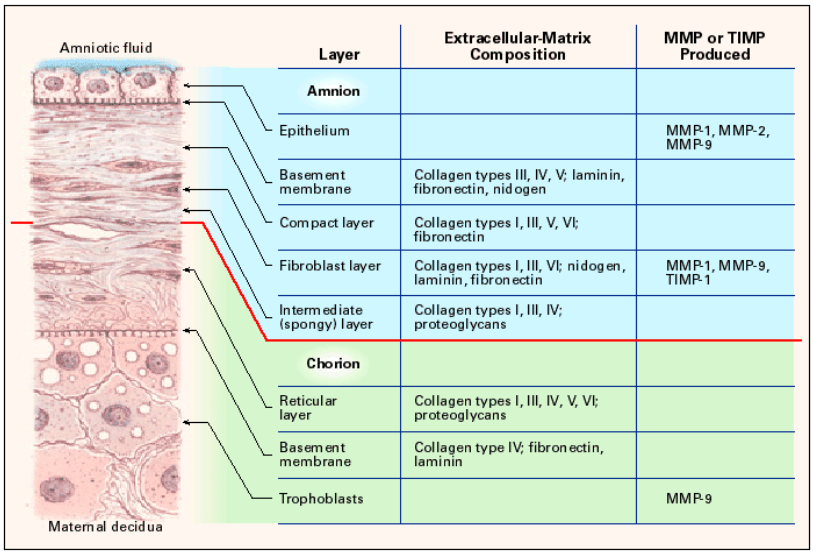
The amniotic sac obliterates the space between it and the chorion by 10-12 weeks of gestation and by 16 weeks the chorioamnion has pushed up against the decidua of the uterine wall **(Calvin and Oyen, 2007).**

Development of the chorion:

In early pregnancy, the villi are distributed over the entire periphery of the chorionic membrane. A blastocyst dislodged from the endometrium at this stage of development appears shaggy. As the blastocyst with its surrounding trophoblasts grows and expands into the decidua, one pole extends outward toward the endometrial cavity. The opposite pole will form the placenta from villous trophoblasts and anchoring cytotrophoblasts. Chorionic villi in contact with the decidua basalis proliferate to form the chorion frondosum which is the fetal component of the placenta. As growth of embryonic and extraembryonic tissues continues, the blood supply of the chorion facing the endometrial cavity is restricted. Because of this, villi in contact with the decidua capsularis cease to grow and degenerate. This portion of the chorion becomes the avascular fetal membrane that abuts the decidua parietalis, that is, the chorion laeve. Until near the end of the third month, the chorion laeve is separated from the amnion by the exocoelomic cavity. Thereafter, they are in

intimate contact to form an avascular amniochorion. With continued expansion of the embryo–fetus, the uterine lumen is obliterated, and the chorion laeve becomes contiguous with the entire maternal decidua parietalis that is not occupied by the placenta. As the fetus grows, the decidua capsularis merges with the parietalis. The capsularis then is largely lost by pressure and the attendant loss of blood supply. The area of decidua where decidua capsularis and decidua parietalis merge is referred to as the decidua vera **(Cunningham et al., 2010).**

Histology of the amnion:



Layer	Extracellular-Matrix Composition	MMP or TIMP Produced
Amnion		
Epithelium		MMP-1, MMP-2, MMP-9
Basement membrane	Collagen types III, IV, V; laminin, fibronectin, nidogen	
Compact layer	Collagen types I, III, V, VI; fibronectin	
Fibroblast layer	Collagen types I, III, VI; nidogen, laminin, fibronectin	MMP-1, MMP-9, TIMP-1
Intermediate (spongy) layer	Collagen types I, III, IV; proteoglycans	
Chorion		
Reticular layer	Collagen types I, III, IV, V, VI; proteoglycans	
Basement membrane	Collagen type IV; fibronectin, laminin	
Trophoblasts		MMP-9

Fig. (1): Schematic representation of the structure of the fetal Membranes at Term. The extracelluar-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).***