International Journal of Gynecology and Obstetrics (2006) **93**, 18—21

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

# Amniotic fluid endothelin levels and the incidence of premature rupture of membranes

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Received 17 September 2005; received in revised form 13 December 2005; accepted 15 December 2005

**KEYWORDS**
Endothelin;
Premature rupture of membranes;
Amniotic fluid

**Abstract**

*Objective:* The purpose of this prospective study was to record Endothelin 1 (ET1) concentrations in the second trimester amniotic fluid and in women who develop premature rupture of membranes (PROM), preterm premature rupture of the membranes (PPROM) and in women with uneventful pregnancies. *Method:* Amniotic fluid was retrieved by amniocentesis from 125 women in the second trimester of pregnancy. The levels of Endothelin were measured by a sensitive and specific radioimmunoassay. *Results:* From the 125 women included in the study 20 developed PROM and preterm PROM (13 PPROM and 7 PROM). The ET1 concentration was significantly higher ($P<0.001$) in PROM and PPROM than in normal pregnancy (96.4 vs. 43 pg/ml). The sub-analysis of the two rupture of membranes groups found that the concentration of ET1 was higher in the PPROM than in PROM (118 vs. 72 pg/ml). *Conclusion:* The amniotic fluid concentration of ET1 is elevated by the second trimester in women who later develop preterm PROM or term PROM.


## 1. Introduction

Endothelin is a protein molecule that has a variety of physiological roles within the human body. It is known to be part of a larger family of similar protein based molecules. Within this family three different types of Endothelin molecules have been identified termed Endothelin 1, 2 and 3. Endothelin has been noted to be present within the amniotic fluid of humans. It is believed to be synthesized within amniocytes cells [1]. Its exact roles in relation to human reproduction are still largely an enigma. Maternal and fetal plasma concentrations of Endothelin have been recently studied with respect to pregnancy associated pathological processed. These include intrauterine growth restriction (IUGR), pre-

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doi:10.1016/j.ijgo.2005.12.013

eclampsia and intrauterine passage of meconium [2—4]. The exact mechanisms for these pathological processes and the increased Endothelin plasma concentrations is still largely unknown, although there is evidence to suggest Endothelin is associated with endothelial cell damage as in pre-eclampsia [2] and also has intertwining roles with the leptin system in the fetus [3]. There is very limited research to date assessing Endothelin in the second trimester amniotic fluid as a marker for future pregnancy associated pathological processed. A recent study suggested that amniotic Endothelin concentration could be used as a predictor of future development of severe pre-eclampsia [5].

Premature (PROM) and preterm premature rupture (PPROM) of membranes are an extremely important yet common event in pregnancy. Both these events can significantly effect the management of that pregnancy.

The premature rupture of membranes (PROM) is defined as rupture of the membranes with a latent period before the onset of spontaneous uterine activity When the PROM occurs before 37 completed weeks of gestation then the condition is referred as preterm premature rupture of membranes (PPROM) [6].

PPROM is particularly important as it complicates about one third of the preterm deliveries [6]. It affects 120,000 deliveries in the United States per annum [7]. It is known that premature delivery before 37 occurs for less than 10% of pregnancies but accounts for more than 60% of all neonatal deaths in developed countries [6]. A variety of investigative tools have been used to increase the accuracy of diagnosing PPROM and PROM [8,9]. Although there has been great developments made to create diagnostic tools for the diagnosis of PPROM and PROM there is no validated predictor of PPROM and PROM before it has happens. There would be significant advantages to be able to predict PPROM and PPROM before it occurs. This would allow the opportunity for early active management, timely counselling, an opportunity for greater understanding of this process and possible prevention. There has been great interest into this area but limited results to date [10].

Endothelin may have an important role to play in the pathogenesis of rupture of the amniotic membranes. Endothelin has been noted to have the capacity to generate uterine contraction in animal models, activate phospholipase A2 and phospholipase, which are associated with rupture of membranes [11,12]. It has been noted that Endothelin 1 and 2 are increased in the amniotic fluid of pregnancies once premature labor has occurred [13]. There have been no studies to date recording the concentration of Endothelin in the amniotic fluid with rupture of membranes. There have also been no studies looking at second trimester amniotic fluid Endothelin concentration as a marker of future rupture of membranes.

The objective of this prospective observation study was to record the concentration of amniotic fluid Endothelin 1 at the time of amniocentesis at 15 to 17 weeks gestation and compare with the incidence of PROM and PPROM.

## 2. Methods

A prospective observation study was carried out on 125 consecutive women attending for booking antenatal screening with a live singleton pregnancy. The reason for screening was the advanced maternal age (over 35 years old) or the previous abnormal screening. All women who required and requested amniocentesis were invited to participate in the study. All women initially underwent an early dating ultrasound scan at 10 to 12 weeks gestation to allow accurate gestational dating. Exclusion criteria included woman with previous: premature deliveries, premature rupture of membranes, hypertension, pregnancy-induced hypertension, pre-eclampsia and diabetes mellitus. Pregnancies with fetal chromosomal abnormalities and congenital malformations were also excluded from the study. This was applied to decrease the incidence of potential confounding variables. These potential confounding variables were identified after literature review. The local ethical committee and the department of obstetrics and gynecology approval were obtained prior to commencement of the study. Informed consent was obtained with the aid of interview and patient information leaflets.

125 consecutive women agreed to participate in the study. Recruitment was performed at the time of amniocentesis. Within the study group 7 women developed later in pregnancy PROM and 13 PPROM.

The control group (88 patients) had uncomplicated pregnancy.

A transabdominal approach was performed on all ladies via a 35-gauge needle. A 5 ml aliquot was obtained at 15 to 17 weeks of gestation during the amniocentesis for the antenatal screening. All samples were cultured for aerobes anerobes, ureaplasma, mycoplasma, and Chlamydia. The sample was collected in EDTA tubes and centrifuged at 3000 revolutions per minute for 5 min. The fluid was separated from the cell sediment and frozen at −70 °C. The levels of Endothelin 1 (ET 1) were quantified with the aid of an enzyme immunoassay kit (Amersham Ednothelin 1 specific assay system with Amerlex-M tm magnetic separation). The assays were