Research Article

The Role of Tumor Necrosis Factor-α (TNF-α) and Matrix Metalloproteinase-9 (MMP-9) Serum in Preterm Premature Rupture of Membranes

Peran Tumor Necrosis Factor-α (TNF-α) dan MMP-9 Serum pada Ketuban Pecah Dini Kehamilan Preterm dan Kehamilan Preterm tanpa Ketuban Pecah Dini

Ardiles[1], Desmiwarti[1], Hafni Bachtiar[2]

[1]*Department of Obstetrics and Gynecology*
[2]*Faculty of Medicine, Universitas Andalas/*
Dr. M. Djamil Hospital
Padang

Abstract

Objective: To investigate the role of TNF-α and MMP-9 serum in preterm premature rupture of membranes (PPROM).

Methods: We used cross-sectional study design. Subjects were all pregnant women with and without PPROM who underwent check up at Obstetrics and Gynecology Functional Medical Staff General Hospital Dr. M. Djamil and networking hospital.

Results: A total of 48 subjects were enrolled in this study. The mean serum levels of TNF-α in patients with PPROM 17.43 ng/ml ± 12.4 ng/ml and without PPROM 8.45 ng/ml ± 6.86 ng/ml. The mean serum levels of MMP-9 in patients with PPROM 8.77 ng/ml ± 4.41 ng/ml, and without PPROM 4.46 ng/ml ± 3.04 ng/ml. Statistical test result p value <0.05, it can be conclude there are differences in the levels of TNF-α and MMP-9 serum in premature rupture of membranes and without premature rupture of membranes pregnancy of preterm.

Conclusion: There are differences in the levels of TNF-α and MMP-9 serum in PPROM and without PPROM.

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Keywords: MMP-9, premature rupture of membranes, TNF-α

Abstrak

***Tujuan**: Mengetahui perbedaan kadar TNF-α dan MMP-9 serum pada ketuban pecah dini dan tanpa ketuban pecah dini kehamilan preterm.*

***Metode**: Penelitian dilakukan dengan desain potong lintang. Populasi penelitian semua ibu hamil dengan Ketuban Pecah Dini dan tanpa Ketuban Pecah Dini kehamilan preterm yang melakukan pemeriksaan ke SMF Kebidanan dan Kandungan RSUP Dr. M. Djamil dan Rumah Sakit jejaring. Total sampel 48 orang. Analisis data dilakukan dengan uji T independen.*

***Hasil**: Rerata kadar serum TNF-α pada pasien ketuban pecah dini kehamilan preterm 17,43 ng/ml± 12,4 ng/ml dan tanpa ketuban pecah dini 8,45 ng/ml± 6,86 ng/ml. Rerata kadar serum MMP-9 pada pasien ketuban pecah dini kehamilan preterm 8,77 ng/ml ± 4,41 ng/ml, dan tanpa ketuban pecah dini 4,46 ng/ml ± 3,04 ng/ml. Hasil uji statistik didapatkan nilai p < 0,05 maka disimpulkan terdapat perbedaan kadar serum TNF-α dan MMP-9 pada ketuban pecah dini dan tanpa ketuban pecah dini kehamilan preterm.*

***Kesimpulan**: Terdapat perbedaan kadar serum TNF-α dan MMP-9 pada ketuban pecah dini dan tanpa ketuban pecah dini kehamilan preterm.*

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***Kata kunci**: ketuban pecah dini, MMP-9, TNF-α*

Correspondence: Ardiles, dr.ardiles86@gmail.com

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is an important issue in the obstetric field because it is associated with birth complications by the means of prematurity and infections to sepsis with chorioamnionitis increases the impact of perinatal morbidity and mortality and maternal.[1]

Preterm birth is defined as birth before 37 weeks gestation. The incidence of preterm birth is approximately 9.6% worldwide. The incidence of preterm delivery in developing countries of varies from 5 to 9%.[2] Preterm birth is a multifactorial disorder. Numerous factors may cause preterm labor, including infection, uterine overdistention, ischemia utero placenter, endocrine factors, cervical abnormalities and immunological abnormalities that sparked the birth preterm.[3]

The Infant Mortality Rate (IMR) was 35/1000 live births (in the 2002-2003) to 34/1000 live births in 2012. Infant mortality rate (IMR) of West Sumatra (27/1000 live births) is ranked fifth from all provinces in Indonesia. Infection is still the major cause of infant death.[4]

The incidence of PPROM is 8-10% in pregnant women, and according to the Journal of Health Sciences Management and Public Health in 2006, the incidence of the PPROM varied between 4% - 14%, with 30% - 40% of cases are preterm, resulting in infant morbidity and mortality.[5]

PPROM incidence rate ranges from 2 to 18% of pregnancies, while the latest report shows the incidence rate of 14-17% of pregnancies. In term pregnancies incidence rate of approximately 5-18% of labor.[6]

PPROM is no sign of rupture before labor. Premature rupture of the amniotic fluid is discharge (amniotic fluid) prior to the onset of labor. Several factors contributing to PPROM include infection, smoking, and psychological stress factors maternal.[1]

PPROM has been linked to infection with the etiologic main form of chorioamnionitis. Therefore, an understanding of mechanisms of inflammation in chorioamnionitis will help prevent PPROM. The amnion is the inner lining of the fetal membranes that limit the amniotic cavity. The amnion consisting of a layer of epithelial cells above the basal membrane is thicker and spongy layer of collagen that contains mesenchymal cells. The amnion is a part of the formation of the fetus and can protect the fetus from mechanical injury by wrapping it in the amniotic fluid. Amniotic draws its strength from collagen, particularly collagen type IV, in the basal membrane. Collagen in the basement membrane and collagen-collagen degradation are in korioamnion controlled by matrix metalloproteinases (MMP). MMP-1 degrades collagen type I, II and III, while MMP-2 and MMP-9 (gelatinase B) degrades collagen type IV. In chorionic cells in humans, tumor necrosis factor alpha (TNF-α) has been shown to induce the production of MMP and prostaglandin E2 (PGE2), and pressing the tissue inhibitor of metalloproteinases (tissue inhibitors of metalloproteinases [TIMP]). Thus, TNF-α has a tendency to cause weakening and rupture of the membrane through the degradation of the collagen matrix of extracellular.[7]

Elevated TNF-α levels may trigger the expression of MMP-9, thereby leading to increased degradation of type IV collagen in the membranes of pregnant women, which often cause PROM. Fortuno 1999 stated that TNF-α triggers the expression of MMP-9 in cells hAE. These results are partially consistent with a previous report that the in vitro secretion of TNF-α trigger MMP-9 in human amnion and the trophoblast.[7] This study is aimed to investigate the role of TNF-α and MMP-9 serum in premature rupture of membranes (PPROM)

METHODS

We used cross-sectional study design. Subjects were all pregnant women with and without PPROM who underwent routine check up to Obstetrics and Gynecology Functional Medical Staff General Hospital Dr. M. Djamil and networking hospital. Total sample of 48 people.

RESULTS

The results of this study could be seen by the presentation of the following mean differences in the levels of TNF-α and MMP-9 serum in (PPROM) and those without PPROM can be seen in Table 1 and 2.

Table 1. The Mean Differences in the Levels of TNF-α Serum in Pregnancy of Preterm Premature Rupture of Membranes and without Premature Rupture of Membranes

TNF-α Level	**n**	**Mean ± SD**	***p value***
Preterm Premature Rupture of Membranes	24	17.43 ± 12.40	0.004
without Premature Rupture of Membranes	24	8.45 ± 6.86	

Table 1 shows the mean serum levels of TNF-α in patients with PPROM 17.43 ng/ml ± 12.4 ng/ml and without PPROM 8.45 ng/ml ± 6.86 ng/ml. Statistical test result p value <0.05, it can be conclude there are differences in the levels of TNF-α serum in premature rupture of membranes and without premature rupture of membranes pregnancy of preterm.

Table 2. The Mean Differences in the Levels of MMP-9 serum in Pregnancy of Preterm Premature Rupture of Membranes and without Premature Rupture of Membranes

MMP-9 Level	n	Mean ± SD	*p value*
Preterm Premature Rupture of Membranes	24	8.77 ± 4.41	0.000
without Premature Rupture of Membranes	24	4.46 ± 3.04	

Table 2 shows the mean serum levels of MMP-9 in patients with PPROM 8.77 ng/ml ± 4.41 ng/ml, and without PROM 4.46 ng/ml ± 3.04 ng/ml. Statistical test result p value <0.05, it can be conclude there are differences in the levels of MMP-9 serum in premature rupture of membranes and without premature rupture of membranes pregnancy of preterm.

DISCUSSION

We found that the mean serum levels of TNF-α in patients with PROM were higher compared to the mean levels of serum TNF-α pregnancy of preterm pregnancy with PPROM (p = 0.04). Pro-inflammatory cytokines, such as TNF–α are thought to play an important role in PROM by altering the status to the active state. Cytokines stimulate the activity of the membranes through the production of uterine activation proteins (UAPs), particularly PGF2a and its receptor, MMPs, VEGF, and oxytocin receptor. TNF-α, for example, increases the production of PG *in vitro* by the stimulation of endometrial and trophoblastic cyclooxygenase-2 (COX-2) expression as well as by reducing PG 15-hydroxy PG dehydrogenase that converts into inactive metabolites. PG-dependent increase in cytokines induces uterine contractions and activate MMPs such as MMP-2 and MMP-9 that degrade extracellular matrix of chorio-amniotic membranes. Another important protein that is stimulated by TNF-α is the possibility of increasing the production of cortisol due to placental releasing hormone (CRH) is involved in preterm premature rupture of membranes. Increased cortisol TNF-α dependent inhibition achieved by placental 11p-hydroxysteroid dehydrogenase, which converts cortisol into cortisone derifat not active.[8]

TNF-α works as endotoxin released by gram-negative bacteria that cause increased production of prostaglandins, endothelin, and realesing cortico-trophin hormone (CRH) in the decidua, chorion and amnion cells. Prostaglandin and endothelin would trigger uterine contractions while simultaneously an increase in the production of prostaglandins in the placenta that is stimulated by CRH. In addition, TNF-α IL-6 induces the expenditure of the decidua and chorionic cells. IL-6 will increase the secretion of prostaglandins and endothelin. TNF-α also triggers the secretion of matrix metalloproteinase (MMP) of the chorion and cervical cells that will induce the degradation of the extracellular matrix of the lower uterine segment and this will cause an inflammatory response. This will trigger the activation and recruitment of granulocytes which will issue elastase high concentrations will cause a reduction of the extracellular matrix, it will lead to premature rupture of membranes delivery preterm.[9]

The survey results revealed that the mean serum levels of MMP-9 in patients with PPROM is higher at 8.77 ng/ml with a standard deviation of 4.41 ng/ml, compared to the mean levels of serum MMP-9 pregnancy of preterm premature rupture of membranes without which 4.46 ng/ml with a standard deviation of 3.04 ng/ml. Statistical test result p value = 0.000 (p value <0.05), it can be concluded there are differences in serum levels of MMP-9 in the pregnancy of preterm premature rupture of membranes and preterm pregnancies without premature rupture of membranes.

Apoptosis and increased expression of MMP is an important key to the integrity of the membrane. Accurate description of activation of membrane rupture is not yet available, but the extracellular matrix degrading enzymes (MMP) such as MMP-1, MMP-8, MMP-9, and neutrophil elastase has an effect on the process. These enzymes cause stretching of the membrane that ultimately led to the rupture of the membrane. Excessive expression and activation of multiple types of MMP before delivery may result in localized damage to the tissue extracellular matrix and cell apoptosis decidua membrane that is clinically called premature rupture of membranes. Class of gelatinase MMP such as MMP-2 and MMP-9 have a high proteolytic activity against type IV collagen, ie collagen building basement membrane and its

expression in amnion increases as we enter the time of delivery. Increased MMP-9 levels also have an impact on the degradation of the extracellular matrix and amnion epithelial cell apoptosis process that ultimately led to the process of stretching and rupture of membranes. In the early stages of collagen catabolism mediated by MMP-1, which will generate fragments are further degraded by MMP back other types of classes include gelatinase MMP such as MMP-2 and MMP-9.[10]

Excessive expression and activation of multiple types of MMP before delivery may result in localized damage to the tissue extracellular matrix and cell apoptosis decidua membrane that is clinically called premature rupture of membranes. Class of gelatinase MMP such as MMP-2 and MMP-9 have a high proteolytic activity against type IV collagen, ie collagen building basement membrane and its expression in amnion increases as we enter the time of delivery. Increased MMP-9 also have an impact on the degradation of the extracellular matrix and amnion epithelial cell apoptosis process that ultimately led to the process of stretching and rupture membrane.[11]

MMP-9 is an important intermediary in the pathological processes that lead to preterm premature rupture of membranes. At the time of delivery, MMP-9 is the major MMP responsible for gelatinolytic activity in membranes. MMP-9 is able to degrade type IV collagen components main of basement membrane amnion, MMP will no doubt have an involvement in the growth and overhaul the membranes normal during pregnancy and in the weakening and rupture of the membranes at the onset of contractions and delivery takes place. In addition, the MMP also play a role in pathological processes KPD, preterm PPROM and preterm delivery spontaneous.[12]

In the case of PPROM, TNF-α and other pro-inflammatory cytokines play a role in stimulating uterine activity and fetal membranes by the means of producing prostaglandins, cortisol and degrades the extracellular matrix of the membranes through the MMP-2 and MMP-9. In preterm premature rupture of the levels of TNF-α and other pro-inflammatory cytokines such as IL-1β in the amniotic fluid found increased.[1]

CONCLUSIONS

The mean serum levels of TNF-α in patients with PPROM 17.43 ng/ml ± 12.4 ng/ml and without PPROM 8.45 ng/ml ± 6.86 ng/ml. The mean serum levels of MMP-9 in patients with PPROM 8.77 ng/ml ± 4.41 ng/ml, and without PPROM 4.46 ng/ml ± 3.04 ng/ml. Statistical test result p value <0.05, it can be conclude there are differences in the levels of TNF-α and MMP-9 serum in PPROM and without PPROM.

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