

# MATRIX METALLOPROTEINASE 7 (MMP-7) LEVEL ON A TERM PREGNANCY ON PRIMIGRAVID AND MULTIGRAVID IN SERVICOVAGINAL FLUID

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## ABSTRACT

In normal pregnancy, the human cervicovaginal fluid proteome is a picture of the local biochemical environment and is influenced by physical changes that occur in the vagina, cervix, and surrounding fetal membranes. Normal pregnancy is associated with hemodynamic signs and changes in the uterus followed by adequate uteroplacental blood flow and development of the uterus for fetal growth.<sup>3</sup> Normal pregnancy is associated with significant uterine and vascular remodeling. Matrix metalloproteinase (MMP) is the main regulator of tissue remodeling. This shows that MMP plays a role in uteroplacental and vascular remodeling during normal pregnancy.

This study is an analytical study using a cross sectional design to assess differences in MMP-7 levels in primigravid and multigravid pregnant women at delivery at the Adam Malik General Hospital in Medan and the USU FK network hospital. The study population was at term primigravid and multigravid pregnant women during labor in the delivery room, with samples of primigravid and multigravid pregnant women at delivery in the delivery room of the General Hospital. H. Adam Malik Medan and USU FK network hospital. Pregnant women who meet the research criteria as mentioned above, included in the subject of pregnancy during labor latent and active phase.

It was found that an increase in MMP-7 level in primigravid and multigravid on latent and active phases, so it can be concluded that MMP-7 affects the duration of cervical maturation, the duration of the latent phase and the active phase in primigravid and multigravid, this indicates an increase in MMP-7 levels with ( $p < 0.001$ ), this indicates a significant relationship between increased levels of MMP-7 with cervical maturation and the duration of the latent and active phases in primigravid and multigravid.

**Kata Kunci:** MMP-7, labor, latent phase, active phase.

## Introduction

Labor occurs at the end of gestation and various processes are involved in cervical ripening, myometrial contractions, torn amniotic membranes and separation from the placenta. This is coordinated by many factors such as hormones and inflammatory mediators. A number of tissues suffer damage, repair and remodeling during labor, placental detachment and uterine involution.<sup>1,2</sup>

In pregnancy, the human cervicovaginal fluid proteome is a picture of the local biochemical environment and is influenced by physical changes that occur in the vagina, cervix, and surrounding fetal membranes. Normal pregnancy is associated with hemodynamic signs and changes in the uterus followed by adequate uteroplacental blood flow and development of the uterus for fetal growth.<sup>3</sup> Normal pregnancy is associated with significant uterine and vascular remodeling. Matrix metalloproteinase (MMP) is the main regulator of tissue remodeling. This shows that MMP plays a role in uteroplacental and vascular remodeling during normal pregnancy.<sup>4</sup>

During pregnancy, the uterus enlarges to accommodate the development of the fetus, amniotic fluid, and placenta. During labor, the extracellular matrix (ECM) undergoes an overhaul to prepare for uterine contractions and after delivery, the uterus revolution. This process occurs due to the rapid collagen degradation process and the rearrangement process during pregnancy. Degradation and remodeling of the extracellular matrix is mediated by proteolytic enzymes which are essential enzymes in labor. MMP in this case plays an important role in this process considering the substrate it produces.<sup>4</sup>

In study of Li et al mentioned that during normal pregnancy, MMP-7 will increase during the 2nd and 3rd trimesters of pregnancy. Increased concentration with increasing gestational age indicates MMP-7 levels are increasing along with increasing gestational age which MMP-7 is associated with preparation for cervical ripening to prepare for labor.<sup>5</sup>

The amniotic membrane and cervix consist of special cells and extracellular matrix that form complex and multi-laminar tissue. The greater the pregnancy, the cervix will undergo extracellular matrix remodeling to adjust the changes in the size of the fetus, to adjust the cervix for labor or also called the process of cervical maturation. Geng et al mentioned that the increase in MMP expression in the cervix and amniotic fluid is related to the reduced strength of the cervical tension, which in turn will cause the opening of the cervix and rupture of the membranes.<sup>4</sup>

MMP-7 accumulation is also known to increase during and after delivery. During labor, the cervix remains closed and stiff to prevent the passage of immature fetuses through the birth canal. During labor, the cervix must be dilated and wide open to be passed by a mature and viable fetus.<sup>4</sup>

Shifts in this process during pregnancy can cause pathological conditions. As in premature labor and prolonged labor. This may also affect differences in primigravid and multigravid delivery. The duration of the latent phase and the active phase of primigravid and multigravid differ in time. In multigravid, extracellular remodeling influences preparation for cervical maturity. In multigravid, the strength of the uterine tension is not as strong as the cervical tension in primigravids. This is due to the cervical remodeling process that cannot return the extracellular matrix composition as in the initial composition. This difference in composition is also most likely related to differences in the level of cervical maturity in primigravid and multigravid. In pregnancy, the human cervicovaginal fluid proteome is a picture of the local biochemical environment and is influenced by physical changes that occur in the vagina, cervix and surrounding fetal membranes. The metalloproteinase (MMP) matrix is the main regulator of tissue remodeling.<sup>4</sup> This makes researchers interested in examining differences in levels of MMP-7 in primigravid and multigravid. This study aims to determine differences in MMP-7 levels in pregnant women during primigravid and multigravid deliveries at H Adam Malik General Hospital Medan and USU FK network hospital.

## Material and Methods

This study is an analytical study using a cross sectional design to assess differences in MMP-7 levels in primigravid and multigravid pregnant women at delivery at the Adam Malik General Hospital in Medan and the USU FK network hospital. The study population was at term primigravid and multigravid pregnant women during labor in the delivery room, with samples of primigravid and multigravid pregnant women at

delivery in the delivery room of the General Hospital. H. Adam Malik Medan and USU FK network hospital. Pregnant women who meet the research criteria as mentioned above, included in the subject of pregnancy during labor latent and active phase. Furthermore, all research subjects are managed at USU Integrated Laboratory. The steps taken in the sample are history taking, including name, age, parity, first day of last menstruation. Then do a physical examination, including awareness, weight and height, blood pressure, and ultrasound according to fixed procedures. The research procedure was that the swab was removed into the cervix and the posterior fornix approximately 20 seconds. Each swab is placed in a test tube containing 0.5 ml of phosphate-buffered saline and rinsed in a buffer for 10-15 seconds. Samples were centrifuged for 20 minutes at  $3000 \times g$  at  $2-8^{\circ}\text{C}$ . Polyester cotton absorbs about 150 ml of liquid when it is saturated, and the average dilution of a vaginal / cervical sample in a buffer is about 1: 5. The specimen is frozen and stored at  $-20^{\circ}\text{C}$ . Supernatants are valued in ng / mL.

## Result

A total of 60 samples were found that met the inclusion criteria, and agreed to participate. Subjects consisted of 30 people in primigravid with 15 people in the active phase and 15 people in the latent phase. And 30 people in multigravid with 15 people in the active phase and 15 people in the latent phase. It was found that the respondents in this study consisted of 2 groups, primigravid, with an average age range of  $28 \pm 4$  and multigravid with an average age of  $30 \pm 4$ . Found 15 (48.3) came with a latent phase in primigravid and 16 (51.6) in the active phase, whereas in multigravid 15 (51.7) came in the latent phase and 14 (48.2) in the active phase. The mean MMP-7 in primigravid was  $0.29 \pm 0.47$  and  $2.12 \pm 2.48$  in multigravid. In primigravid the mean opening of patients was  $3 \pm 2$  and  $4 \pm 2$  in multigravid. The duration of labor in primigravid is  $10 \pm 4$  and  $6 \pm 2$  in multigravid. The mean body weight in primigravid was  $50 \pm 6$  and  $51 \pm 7$  in multigravid.

**Tabel 1. Characteristic of Subject**

Variable	Gravida		p
	primigravid	Multigravid	
Age (mean $\pm$ sd)	$28 \pm 4$	$30 \pm 4$	0.704*
Phase (n,%)			
Laten	15 (50)	15 (50)	0.5*
Active	15 (50)	15 (50)	0.5*
MMP-7; pg/ml (mean $\pm$ sd)	$0.29 \pm 0.47$	$2.12 \pm 2.48$	0.001*
Dilatation; cm (mean $\pm$ sd)	$3 \pm 2$	$4 \pm 2$	0.001*
Labor duration; time (mean $\pm$ sd)	$10 \pm 4$	$6 \pm 2$	0.001*
Body Weight; kg (mean $\pm$ sd)	$50 \pm 6$	$51 \pm 7$	0.403*

Based on table 2, obtained MMP-7 average subjects primigravida phase  $0.00 \pm 0.001$ . The mean MMP-7 level of subjects in the latent multigravida phase was  $0.42 \pm 0.084$ . The results showed differences in MMP-7 levels were questioned between different groups.

**Table 2. Comparison of latent phase MMP-7 levels in primigravid and multigravid women**

Labor Phase	Paritas	Mean SD pg/ml	P
Laten Phase	Primigravid	0.00 ± 0.001	< 0.001*
	Multigravid	0.42 ± 0.084	

\*Chi-Square

Based on table 3, it was found that the average MMP-7 level of active phase primigravid subjects was  $0.02 \pm 0.004$ . The average MMP-7 level of active phase multigravid subjects was  $4.24 \pm 1.67$ . The results showed that there were significant differences in MMP-7 levels between the two different parity groups. While in the table above it was found that MMP-7 levels had a positive correlation with opening with r values of 0.924 and values ( $p < 0.001$ ). Whereas with the duration of labor, MMP-7 levels had a negative correlation with r -0.930 with a value ( $p < 0.001$ ). This shows that MMP-7 has a strong relationship with the opening and duration of labor. Where the higher levels of MMP-7, the faster the opening and the shorter the duration of labor.

**Table 4. Correlation of MMP 7 levels to opening and duration of delivery**

		r	P
<b>MMP</b>	Opening	0.924*	<0.001**
	Duration	-0.930*	<0.001**

## Discussion

Until now, little is known about the role of MMP, especially MMP-7 in the birthing process. Only a little is known about the expression and regulation of the cervical smooth muscle during pregnancy and term pregnancy. Based on the research, it was found that the respondents in this study consisted of 2 groups, primigravid group, with an average age range of  $28 \pm 4$  and multigravid with an average age of  $30 \pm 4$ . Found 15 (50%) came with a latent phase in primigravid and 15 (50%) in the active phase, whereas in multigravid found 15 (50%) came in the latent phase and 15 (50%) in the active phase. The mean MMP-7 in primigravid was  $0.29 \pm 0.47$  and  $2.12 \pm 2.48$  in multigravid. In primigravid the mean opening of patients was  $3 \pm 2$  and  $4 \pm 2$  in multigravid. The duration of labor in primigravid is  $10 \pm 4$  and  $6 \pm 2$  in multigravid. The mean body weight in primigravid was  $50 \pm 6$  and  $51 \pm 7$  in multigravid.

This is in line with Ayoub's study which showed that more than two thirds (72.2%) of primigravids in their study group had ages ranging from (20-29) years compared to (47.6%) among multigravids and only (5, 6%) primigavida aged over 34 years. compared with (17.6%) among multigravids with a mean age of primigavida ( $24.1139 \pm 5.10904$ ) compared with ( $29.66879 \pm 74224$ ) among multigravids.<sup>5</sup>

Based on the research, it was found that the average MMP-7 level of latent phase primigravid subjects was  $0.00 \pm 0.001$ . The mean MMP-7 level of the latent phase multigravid subject was  $0.42 \pm 0.084$ . The results showed that there were significant differences in MMP-7 levels between the two different parity groups. average MMP-7 levels of active phase primigravid subjects were  $0.02 \pm 0.004$ . The average MMP-7

level of active phase multigravid subjects was  $4.24 \pm 1.67$ . The results showed that there were significant differences in MPMP-7 levels between the two different parity groups, so in this study,  $H_0$  was rejected, and  $H_a$  was accepted.

Yujing et al. In their study showed that the concentration (MMP-7) increased significantly in CVF during labor ( $n = 16$ ) compared to all samples not in labor ( $n = 44$ ,  $P = 0.025$ ).<sup>6</sup>

Saori, in his research also supports the role of MMP-7 in the degradation of ECM in fetal membranes during labor. Junnan Gang The Role and Regulation of the MMP System in the Separation Process, where MMP-7 plays an important role in cervical maturation.<sup>7</sup>

According to Geng, from the results of their study it was said that age and weight did not affect MMP-7 levels. However, MMP-7 is overproduced by the placenta in preeclampsia due to the activity of proteolytic MMPs. Increased MMP-7 can also be found in KPDs that are associated with an inflammatory response.<sup>8</sup>

Based on Garcia's research, age and parity can determine the morphological changes of a pig's cervix, which in multiapara women are wider and longer than nulliparous women. Also changes in tissue composition may affect the elasticity of the cervix, especially in the uterine region. In the cervical lumen can be widened and wavy gradually.<sup>9</sup>

Sundoft in his research found that cervical collagen concentrations increase gradually after delivery, this increase is statistically significant up to 9 months, and is not significant from 9-12 months, from 12-15 months. There are no differences between women with induced labor between women and spontaneous labor. The average concentrations of cervical collagen in primigravid women 3, 6, 9, 12 and 15 (50.6%, 57.9%, 61.0%, 64.1% and 62.5%, there were no significant differences in multigravid women (50.2%, 59.1%, 63.7%, 65.7%, and 66.0% of dry weight,) The same results were found in primiparous women (49.5%, 57.9%, 62.0%, 65.7% and 63.6%) with multiparous women (52.1%, 60.2%, 63.8%, 63.9% and 66.3%) 60

In this study it was found that MMP-7 levels had a positive correlation with opening with  $r$  values of 0.924 and values ( $p < 0.001$ ). Whereas with the duration of labor, MMP-7 levels had a negative correlation with  $r -0.930$  with a value ( $p < 0.001$ ). This shows that MMP-7 has a strong relationship with the opening and duration of labor. Where the higher the MMP-7 level, the faster the opening and shorter duration of labor, so that in this study,  $H_0$  was rejected, and  $H_a$  was accepted. In his research, Geng found that ECM has an important role in multiple biological events during labor, and requires the process of protein synthesis and proteolytic degradation. The enzymes that play a role in proteolysis are (MMP-2 and -9) and collagen (MMP-1 and -8), which play a role in cervical remodeling and rupture of the amniotic membrane. Other MMPs such as MMP-3, -7 and -14 contribute to delivery. An imbalance between MMP and inhibitor during labor can cause PPROM, preeclampsia, pelvic organ prolapse, stress type urinary incontinence in women after childbirth.

In line with Fanjul's research on animal model experiments from loss of MMP function, it is very important to identify several new and unexpected functions of these metalloproteinases. Likewise, these models have been very useful for identification of in vivo substrates from MMP and for the formation of causal relationships between dysregulation of this enzyme and the development of various human diseases.



Even so, a new generation of animal models is still needed to evaluate the function of some MMP family members such as MMP-23, MMP-27 or MT6-MMP which are largely unmarked. Some of these new models will require further research to minimize the possibility of functional redundancy or mechanism compensation among MMP family members.<sup>10</sup>

Wei Li showed MMP-1 and MMP-7 increased in the aorta, uterus and placenta of RUPP vs pregnant mice, MMP collagen substrate 1 increased in the aorta, uterus, and placenta RUPP vs pregnant mice, TNF $\alpha$  sitoin increased MMP-1 and MMP-7 in the aorta, uterus and placenta in pregnant mice, while TNF $\alpha$  antagonists reverse the effects of increased TNF $\alpha$  on MMP in pregnant rat tissue.<sup>11</sup>

In Yujing's research, MMP -1, -2, -3, -7, -8, -12, -13 and TIMP-1 and -2 in humans are associated with spontaneous labor. Where there are no temporal changes at MMP concentrations of -1, -2, -3, -8 and -9 on CVF when reaching labor. MMP-7, TIMPI-1 and -2 concentrations were increased in spontaneous normal delivery with TIMP-1, which showed a large increase compared to TIMP-2. TIMP-1 concentrations in CVF significantly increase at least 1 week before onset of labor. MMP and TIMP on CVF can show immunoreactive proteins that are secreted or leak in supracervical amniochorion, deciduas and cervix. In this study although TIMP-1 and -2 increased during labor, MMP-7 increased sharply from its inhibitors. MMP-7 increases as there is cellular epithelial compartment in the amniotic fluid and decidua, in amniotic fluid, and labor is not associated with MMP-7. However MMP-7 activity was significantly increased in amnion with PROM.<sup>12</sup>

Konrad found MMP-13 and MMP-7 that were in a post partum involution. MMP-13 and MMP-7 in uterine postpartum showed a maximum increase on the 2nd day of labor in the uterus and decreased dramatically 2 days after delivery.<sup>13</sup>

## Conclusion

Based on this research, an increase in MMP-7 levels in primigravid and multigravid in the latent and active phases, so it can be concluded that MMP-7 affects the duration of cervical maturation, the duration of the latent phase and the active phase in primigravid and multigravid, this indicates an increase in levels MMP-7 with ( $p < 0.001$ ), this shows a significant relationship between increasing levels of MMP-7 with cervical maturation and the duration of the latent and active phases in primigravid and multigravid. MMP-7 examination can be done to predict the duration of labor.

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