

## **PERBEDAAN EKSPRESI KOLAGEN TIPE III LIGAMENTUM SAKROUTERINA ANTARA PASIEN PROLAPS UTERI DENGAN PASIEN TANPA PROLAPS UTERI**

*andi rosa irawan*, Ermawati, Hafni Bachtiar  
Obstetrics and Gynecology Department

Fakultas kedokteran universitas andalas, Padang

### **Abstrak**

**Latar Belakang :** Disfungsi dasar panggul merupakan salah satu penyebab morbiditas yang dapat menurunkan kualitas hidup wanita. Prolaps organ panggul dapat disebabkan oleh usia dan proses penuaan, kehamilan, perlukaan sewaktu proses persalinan, paritas, menopause, komposisi jaringan pada seorang wanita, konstipasi, batuk-batuk kronis, atau sering melakukan pekerjaan berat. Meskipun mekanisme terjadinya prolaps organ panggul pada wanita dan faktor-faktor yang menyebabkan kegagalan perbaikan dengan operasi belum sepenuhnya dimengerti. Terdapat beberapa bukti yang mendukung bahwa abnormalitas struktur jaringan penyambung merupakan faktor predisposisi. Kolagen merupakan unsur pokok jaringan penyambung dasar panggul. Metabolisme kolagen yang abnormal telah diidentifikasi dan berhubungan dengan kejadian prolaps organ panggul. Gangguan sintesis dan tipe kolagen memiliki hubungan sebab akibat pada gangguan jaringan penyambung, seperti prolaps organ. Pada kejadian prolaps uteri, perubahan komposisi jaringan pada seorang wanita harus dipikirkan sebagai salah satu penyebab terjadinya prolaps. Salah satu jaringan yang sangat mempengaruhi adalah komposisi jaringan kolagen pada ligamentum sakrouterina yang menopang uterus. Ligamentum sakrouterina adalah ligamen yang memegang uterus agar tidak bergerak, membawa kembali kurva serviks kiri dan kanan melalui anus ke arah tulang sacrum kiri dan kanan. ligamen sakrouterina dapat menahan beban lebih dari 17 kg.

**Metode Penelitian :** Penelitian ini dilakukan dengan metode *cross sectional comparative* di kamar rawat ginekologi RSUP Dr. M. Djamil Padang mulai bulan September 2015 sampai bulan Juni 2016 dengan jumlah sampel 22 orang pasien prolaps uteri dan 22 orang pasien tanpa prolaps uteri, yang memenuhi kriteria inklusi dan tidak didapatkan kriteria eksklusi. Kemudian dilakukan analisa statistik dengan pemeriksaan imunohistokimia kolagen tipe III jaringan ligamen sakrouterina untuk mengetahui perbedaan ekspresi kolagen tipe III antara pasien prolaps uteri dan tanpa prolaps uteri.

**Hasil :** Perbedaan ekspresi kolagen tipe III pada jaringan ligamen sakrouterina didapat bahwa persentase kejadian prolaps lebih tinggi pada ekspresi kolagen yang

positif dibandingkan dengan yang negatif yaitu 63,3% berbanding 21,4%. Secara statistik perbedaan tersebut bermakna bermakna ( $p=0,023$ ).

**Kesimpulan** : Ekspresi kolagen Tipe III ligamentum sakrouterina pada POP lebih positif dibanding yang tanpa POP, Terbukti terdapat perbedaan ekspresi kolagen tipe III pada POP dengan tanpa POP

**Kata Kunci** : kolagen tipe III Ligamen sakrouterina, prolaps uteri, Tanpa prolaps uteri



# PERBEDAAN EKSPRESI KOLAGEN TIPE III LIGAMENTUM SAKROUTERINA ANTARA PASIEN PROLAPS UTERI DENGAN PASIEN TANPA PROLAPS UTERI

*Difference in expression of type III collagen ligament sakrouterina among patients with patients*

*without non uterine prolapse uterine prolapse*

*andi rosa irawan*, Ermawati, Hafni Bachtiar  
Obstetrics and Gynecology Department

Medical Faculty of Andalas University, Padang

## **Abstract**

**Background** : Pelvic floor dysfunction is one cause of morbidity that can degrade the quality of life for women. Pelvic organ prolapse can be caused by age and the aging process, pregnancy, injury during childbirth, parity, menopause, the composition of the tissue in a woman, constipation, chronic cough, or often do heavy work. Although the mechanism of pelvic organ prolapse in women and the factors that led to the failure of the repair operation is not yet fully understood. There is some evidence to support that the structure of the connective tissue abnormalities predisposing factors. Collagen is an essential element of connective tissue of the pelvic floor. Abnormal collagen metabolism has been identified and associated with the incidence of pelvic organ prolapse. Impaired synthesis and collagen types have causality in connective tissue disorders, such as organ prolapse. In the event of uterine prolapse, tissue composition changes in a woman should be considered as one of the causes of prolapse.

**Method** : This research was conducted with a cross-sectional comparative method in gynecology hospital room Hospital Dr. M. Djamil Padang starting in September 2015 until June 2016 with a sample of 22 patients prolap uteri and 22 patients without prolap uteri, who met the inclusion criteria and there is no exclusion criteria. Then performed statistical analysis with immunohistochemistry examination of type III collagen ligament sakrouterina to know the difference between the expression of collagen type III patients without prolap prolap uteri and uteri

**Result** : Differences in the expression of type III collagen in ligaments network sakrouterina found that the percentage of prolap higher in collagen expression positive than negative ones, namely 63.3% versus 21.4%. Statistically significant differences were significant ( $p = 0.023$ ).

**Conclusions** : Type III collagen expression sakrouterina ligament in POP is more positive than those without POP, there are evident differences in the expression of collagen type III without POP POP

**Keywords** : type III collagen sacro uterine ligaments, prolaputeri, non prolap uteri

## INTRODUCTION

Pelvic organ prolapse is also known as the urogenital prolapse, is the reduction of pelvic organs that cause protrusion of the vagina, uterus or both. This situation can damage the walls of the anterior, posterior vagina and uterus or vagina peak, which generally appears as a combination of the above. In 1997, more than 225,000 patients undergo pelvic organ prolapse surgery in the USA (22.7 / 10 000 women). Other studies reveal the estimated 11% of all women are at risk of undergoing pelvic organ prolapse surgery. In the United States, the age of which is associated with the incidence of uterine prolapse surgery are women aged above 50 years, ie 2,7- 3,3 per 1000 women uterine prolapse. Genesis Prolap uteri in Indonesia has not found data. According to the annual report of Department of Obstetrics and Gynecology Hasan Sadikin Hospital in 2007, the

incidence of uterine prolapse during 2007 there were 30 cases.<sup>1</sup> The number of patients with a diagnosis of pelvic organ prolapse Uroginekologi been to Polyclinic Hospital. DR. M. Djamil Padang period January 2007-July 2009 was 173 (76.21%). The number of patients with a diagnosis of pelvic organ prolapse who visited the Gynaecology Clinic Hospital. DR. M. Djamil Padang were only treated poly / Conservative as much as 67.63% and were hospitalized for operative action is 56 (32.37%).<sup>2</sup>

Some of the important factors in the incidence of uterine prolapse is the factor content of collagen tissue composition of age, heavy workload, menopause, childbirth, parity, and obesity. There is evidence to suggest that there is a relationship collagen disorders and major components of the extracellular matrix or the repair mechanism, which affects women to occur prolapse. Collagen may play an important role in determining the physiology and structure of the cervix and uterus tissue in the uterine prolapse. Connective tissue containing collagen, elastic fibers and proteoglycans as the dominant component of the extracellular matrix. Extracellular matrix (ECM) is considered to play an important role in the stability of the network and in regulating the growth and differentiation of the cells. The most important part of the support system such as the pelvic ligaments sakrouterina or because of damage to the pelvic and urogenital diaphragm. Sakrouterina ligament is the ligament that holds the uterus that does not move, bring back the cervical curve of the left and right through the anus toward the sacrum bone left and right. In the study suggests that sakrouterina ligaments can withstand a load of more than 17 kg.<sup>3</sup>

A critical element of this is the number of tissue stability and structure of connective tissue formed by fibroblast cells and extracellular matrix. The contents of the extracellular matrix protein that forms the main connective tissue, ie collagen. Extracellularmatrix also contains glycosaminoglycans such as tenascin, fibronectin and laminin. Collagen determine the strength of the network and glycoproteins, such as tenascin play a role in cell adhesion to collagen, wound healing and tumor process. The relationship between the content of collagen and tenascin-C with the incidence of uterine prolapse and its comparison with patients without uterine prolapse still have a bit of data. Fill dimanusia tenascin-C is found in the central nervous system, smooth muscle and ligaments. Tenascin-C is a protein to play a role in cell adhesion processes fibroblast collagen.<sup>3</sup>

Changes in collagen structure of the uterus is affected by estrogen. Estrogen deficiency can affect biomedical composition, quality, and quantity of collagen. Estrogen can affect the content of the synthesis of collagen by increasing or decreasing the damage. The synthesis of collagen and other extracellular matrix components, quantitatively and qualitatively dependent on the stage of cell growth. In women who suffer from uterine prolapse occurs degradation of collagen in the uterus.<sup>4,5,6</sup>

The balance between synthesis and degradation of collagen is important for maintaining the integrity of body tissues and the tensile strength during tissue remodeling continuous. Degradation depends on the combination of the activity of matrix metalloproteinase (MMP) and release regulation, activation of growth factors, growth factor binding protein, a cell surface receptor and cell adhesion molecules. Collagen degradation depends on the activity of MMPs produced by cells of connective tissue. MMP proteolytic activity is specifically regulated by inhibitors TIMPs, binding stoichiometry for MMPs to inhibit their activity. The balance between MMPs and TIMPs define collagenolysis. Vaginal wall tissue of women with prolapse revealed higher MMP-1 mRNA ratio-to-TIMP-1 and TIMP-1 reduction in the protein expression of the network of controls.<sup>7</sup> Jackson and

colleagues found that women with uterine prolapse experienced a total reduction of collagen as much as 25 percent.<sup>8,9</sup>

MMPs are synthesized intracellularly and as a proenzyme secretion into the extracellular space, which requires a change to the active form for enzymatic activity. Twenty-three members of different MMPs have been identified in humans. Everything can reduce one or more components of the extracellular matrix, but with different specificity. Acid cathepsin cleave collagen fiber depolymerase nearby of crosslink. The combination of the action of the enzyme - the enzyme is able to change all the components of the extracellular matrix.

## MATERIALS AND METHODS

This research was conducted with a cross-sectional comparative method in gynecology hospital room Hospital Dr. M. Djamil Padang starting in September 2015 until June 2016 with a sample of 22 patients prolap uteri and 22 patients without prolap uteri, who met the inclusion criteria and there is no exclusion criteria. Then performed statistical analysis with immunohistochemistry examination of type III collagen ligament sakrouterina to know the difference between the expression of collagen type III patients without prolap prolap uteri and uteri. All patients who met the inclusion criteria were given an explanation about the research. Patients who want to participate in the study filled the consent form which is provided. Inclusion criteria, All patients with uterine prolapse severity (stage III and IV) maintained by the results of the clinical examination, Patients who do not suffer from pelvic organ prolapse which will undergo a hysterectomy because of other diseases, Willing to participate in research and Exclusion criteria, Patients with pelvic malignancy, Patients who had undergone previous surgery pelvic organs, Patients in the use of Hormone Replacement Therapy (HRT) in the long term. Samples were taken from the ligament sacrouterina obtained from hysterectomy. Each biopsy cube measuring 5 mm and continued with the examination of Anatomical Pathology Immunohistochemistry.

Examination was conducted in Anatomical Pathology Laboratory of the Faculty of Medicine, University of Padjadjaran / Hasan Sadikin Bandung. Statistical analysis used Statistical Package for the Social Science (SPSS) version 15.

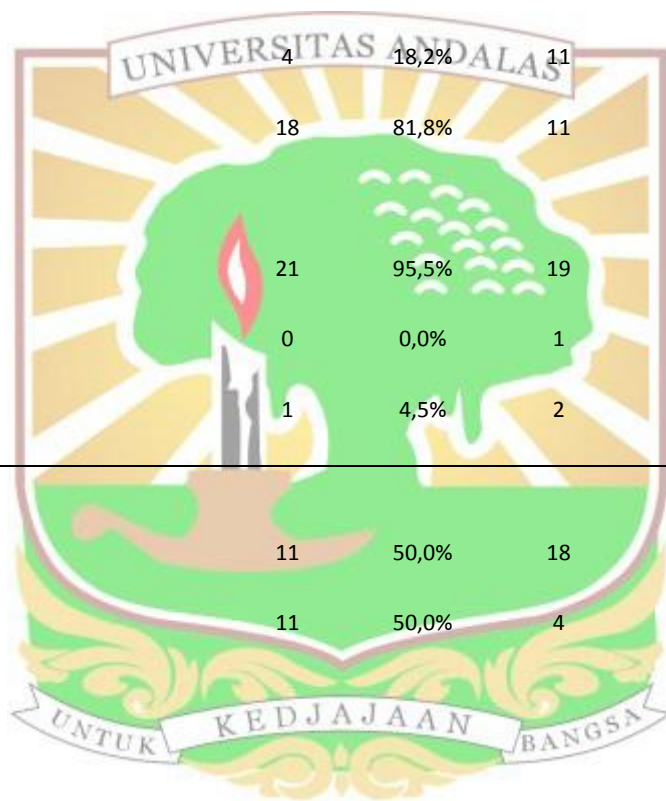
## RESULT

### A. Characteristics of Study Sample

Forty four sample that met the inclusion and exclusion criteria were enrolled. Characteristics of respondents among the group without pelvic organ prolapse and pelvic organ prolapse.

Table 1. Respondent Characteristics Without POP and POP

CHARACTERISTICS	Total				p
	POP		NON POP		
	N	%	n	%	
1	2	3	4	5	6
<b>Age (years)</b>					
≤ 45	2	9,1%	4	18,2%	0,664
> 45	20	90,9%	18	81,8%	
<b>Paritas</b>					
<3	4	18,2%	11	50,0%	0,056
≥ 3	18	81,8%	11	50,0%	
<b>History Type delivery</b>					
Normal parturition	21	95,5%	19	86,4%	0,488
Vakum	0	0,0%	1	4,5%	
Sectio Caesarian	1	4,5%	2	9,1%	
<b>History of delivery</b>					
≤ 3500 gram	11	50,0%	18	81,8%	0,056
> 3500 gram	11	50,0%	4	18,2%	
<b>Hormonal factors</b>					
Premenopause	2	9,1%	11	50%	0,008
Menopause	20	90,9%	11	50%	
<b>BMI</b>					
Normal 18,5 – 24,99	18	81,8%	17	77,3%	1,0
Obesitas > 25,0	4	18,2%	5	22,7%	



Obtained the respondent's age, parity, history of delivery, birth weight and body mass index (BMI), was not statistically significant ( $p > 0.05$ ) between groups with no prolapse. This shows equality and will not cause a bias in the analysis. There were significant differences (p

<0.05) hormonal factors between the two groups. The likelihood that this will lead to bias in subsequent analysis. In order to ascertain whether there is bias, then conducted further tests (two layers).

Tabel 2. Expression of Collagen Type III relationship with Genesis Prolap based on Hormonal Factors

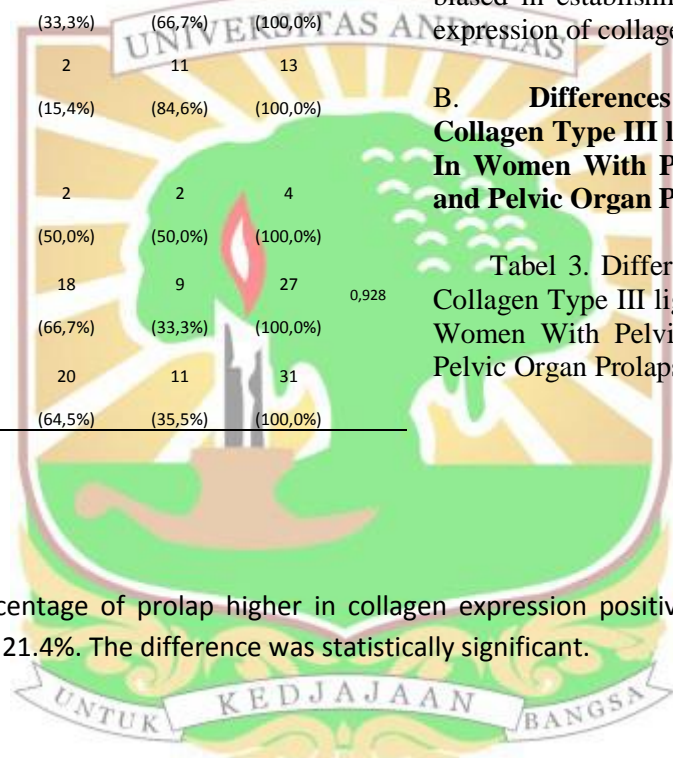
Hormonal Factors	EKSPRESI KOLAGEN III	GROUP		Total	p
		POP f (%)	Non POP f (%)		
Premenopause	Negatif	1 (10,0%)	9 (90,0%)	10 (100%)	0,944
	Positif	1 (33,3%)	2 (66,7%)	3 (100,0%)	
	Total	2 (15,4%)	11 (84,6%)	13 (100,0%)	
Menopause	Negatif	2 (50,0%)	2 (50,0%)	4 (100,0%)	0,928
	Positif	18 (66,7%)	9 (33,3%)	27 (100,0%)	
	Total	20 (64,5%)	11 (35,5%)	31 (100,0%)	

that the relationship with the expression of collagen type III prolapse events, both in premenopausal or postmenopausal, equally significant ( $p > 0.05$ ). Means the different characteristics of hormonal factors not be biased in establishing relations with the expression of collagen III prolapse events.

### B. Differences Expression of Collagen Type III ligament Sakrouterina In Women With Pelvic Organ Prolapse and Pelvic Organ Prolapse Without.

Tabel 3. Differences in Expression of Collagen Type III ligament Sakrouterina In Women With Pelvic Organ Prolapse and Pelvic Organ Prolapse Without.

that the percentage of prolapse higher in collagen expression positive than negative ones, namely 63.3% versus 21.4%. The difference was statistically significant.



## DISCUSSION

### A. Subject Characteristics

Many things in a woman's life turned out to contribute to the occurrence of pelvic organ prolapse, among others age, menopause, parity, type of Delivery, History of the Great Birth, Obesity, Ras Work, chronic pulmonary disease, hormonal disorders, genetic, hysterectomy.<sup>10,11,12,13</sup>

Characteristics age group without pelvic organ prolapse and pelvic organ prolapse show the same picture, which is above 45 years. Where the

EKSPRESI KOLAGEN III	GROUP				Total		p
	POP		Tanpa POP		F	%	
	f	%	f	%			
NEGATIF	3	21,4%	11	78,6%	14	100,0%	0,023
POSITIF	19	63,3%	11	36,7%	30	100,0%	
TOTAL	22	50,0%	22	50,0%	44	100,0%	

average age in the group without prolapse and did not show statistically significant differences. The results of this study differ from research.<sup>11</sup> who get POP level I or II mostly women young age. While POP III and IV level of 2.6% occurred in the age above 40 years, and the prevalence increases to 21% in women aged above 70 years. In this study it was found that there was no difference in age between women with and without pelvic organ prolapse of pelvic organ prolapse.

Characteristics of respondents parity  $\geq 3$  years steeper on without POP POP compared to 81.8% versus 50.0%. Statistically non-significant difference  $p > 0.05$ , which means the two similar groups of POP. Comparing nulliparous and women with high parity. In women with high parity higher risk for genital prolapse compared with women who had never given birth.<sup>13</sup>

Characteristics of hormonal factors are factors that can lead to pelvic organ prolapse. From the analysis of risk factors, postmenopausal status is a significant risk factor of pelvic organ prolapse. This hypothesis is the secondary causes of the various factors involved in it, such as a decrease in estrogen during postmenopause. GD Chen and colleagues discovered estrogen receptors in the vaginal wall and ligament sakrouterina premenopausal women but decreased in postmenopausal women vaginal wall. Reduction of estrogen after menopause period, may have caused the decompensation network.<sup>4,5,6</sup> Estrogen can also affect collagen metabolism by stimulating collagen degradation through increased activity of matrix metalloproteinase-2.<sup>14,15</sup>

## **B. Differences Expression of Collagen Type III ligament Sakrouterina In Women With Pelvic Organ Prolapse and Pelvic Organ Prolapse Without.**

In this study, found that the percentage of pelvic organ prolapse higher in Type III collagen expression positive than negative on the group without pelvic organ prolapse. Increased expression of collagen type III also showed increased elasticity and stretch to the network so that the risk of a larger POP. Therefore, we can conclude that a high amount of collagen III can contribute to the onset of weakness in patients with POP network.

The study of the relationship of collagen III and pelvic organ prolapse are still continuing, therefore the results of this study of collagen still vary. Liapis et al reported the same amount of collagen III in women with or without POP,<sup>16</sup> while Ewiesz et al reported collagen III is elevated in tissues of women with POP and it is supported by several other studies.<sup>17</sup> Difference in this research may be due to differences in the method and place of research tissue.

Collagen III are predominant on the network is needed for increased flexibility and inflation which is the subject of periodic stress. Collagen III is the largest collagen in the skin at birth. Type III is found in granulation tissue during wound healing.<sup>18</sup>

Connective tissue cells synthesize various components of the extra cellular matrix (ECM), which works not only support the special biomechanical and functional properties of the network, but also the regulation of cellular functions. It is impressive that advocates pelvic disorders may be due to an intrinsic abnormality of collagen synthesis or imbalance between synthesis and degradation.<sup>19</sup>



## CONCLUSION

1. Expression of type III collagen ligament in POP sakrouterina more positive than those without a POP.
2. Expression of type III collagen ligament sakrouterina on without POP POP negative than those without.
3. Evidently there are differences in the expression of collagen type III in POP with no POP.

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