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Research Article

Comparing Interleukin 10 (IL-10) Level in Women with Adenomyosis and without Adenomyosis

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Abstract

Background and Objective: Adenomyosis is a disease characterized with heterotrophic stromal and endometrial glands within myometrium surrounded by myometrium hyperplasia. Alterations of immunological system contributed in adenomyosis pathogenesis. One of the cytokines role in adenomyosis pathophysiology is IL-10. This research aimed to investigate the comparison of IL-10 in women with adenomyosis and without adenomyosis. **Materials and Methods:** The research was conducted at Wahidin Sudirohusodo General Hospital and at the network hospitals using the nested case control method. The samples were 37 women with adenomyosis and diagnosed based on the histopathology results and 37 women without adenomyosis. The levels of IL-10 were measured using ELISA method. The data were analyzed using Chi-square test, Mann-Whitney test and Spearman correlation test with the significance of $p = 0.05$. **Results:** The finding of this study indicated that the levels of IL-10 in women with adenomyosis were higher compared to the women without adenomyosis ($p = 0.001$). IL-10 levels has a weak correlation with the incidence of adenomyosis and medium correlation with the size of adenomyosis. **Conclusion:** So it was concluded that there was increased levels of IL-10 in adenomyosis patients compared with no adenomyosis.

Key words: Adenomyosis, heterotrophic stromal, endometrial glands, case control method, adenomyosis pathophysiology

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Adenomyosis is a disorder characterized by the heterotopic stroma and endometrial gland in the myometrium surrounded by myometrial hyperplasia. Adenomyosis is generally found in multiparous ages, such as 40-50 years old, marked by clinical symptoms of pelvic pain and abnormal uterine bleeding which certainly greatly affects the patient's quality of life¹⁻³.

The incidence of adenomyosis varies according to the method of examination and case finding. It was found in clinical cases 10-20%, while based on histopathology examination, it was found 20-40% cases. More than 80% of adenomyosis patients have abnormal uterus, 50% concomitant with uterine myoma, 11% with endometriosis and 7% with endometrial polyps⁴. Many studies have shown that the changes in the immune system have contributed to the pathogenesis of adenomyosis. Endometrial conditions in adenomyosis are different than in healthy women. In women with adenomyosis and endometriosis, estrogen concentration in the blood during menstruation is higher than normal women⁵. Endometrial and leukocyte cells produced cytokines in response to steroid hormones that affect the reproductive process. One of the cytokines that influence the pathophysiology of adenomyosis⁶ is IL-10.

Previous studies by Wang *et al.*⁷ Suggested that this cytokine is produced in abundance by the epithelial cells of ectopic and eutopic endometrium in women with adenomyosis. IL-10 is an anti-inflammatory and immunosuppressive cytokine commonly produced by T-cells or macrophages. IL-10 in the uterus also functions as a mediator in several intrauterine regulations such as progesterone, catecholamines and prostaglandins⁸. IL-10 signal is made through two complex receptors consisting of IL-10 receptor 1 (IL-10R1 or IL-10R α) and IL-10 receptor 2 (IL-10R2 or IL-10R β). The combination of IL-10 receptor complexes is important for suppressing the immune response by inducing signals that cause synthesis inhibition of several cytokines and cellular receptors including TNF- α , IL-1 and IL-6 which are known to play an important role in the pathogenesis and maintenance of adenomyosis^{3,9,10}. It has been reported that IL-10 levels increase significantly in endometriosis patients compared to normal women. However, in the case of adenomyosis there are still less reports showing the same thing. Therefore, this study is designed to reveal whether IL-10 levels, also, increased significantly in adenomyosis patients⁷.

This study emphasizes that it is important to maximize and develop a research on women health include their health care service and medical treatment to decrease a number of medical symptoms and diseases on women. This study indirectly addresses to the importance of keeping insight on women health progress and it becomes the basic reason to conduct this study. Therefore, this study was aimed to determine the ratio of interleukin 10 (IL-10) level in women with adenomyosis and without adenomyosis.

MATERIALS AND METHODS

This research was conducted at the Wahidin Sudirohusodo General Hospital and the network hospitals of obstetrics and gynaecology education at UNHAS (Hassanudin University) in Makassar. This research was conducted in September 2017-February, 2018. This research is a comparative analytic research using a nested case control research design by Ernster¹¹. The research variables consisted of Independent Variables (Interleukin-10), Dependent Variables (Adenomyosis) and Intermediate Variables (HLA-G, Proinflammatory Cytokines). The population in this study were all women diagnosed with adenomyosis and no adenomyosis through histopathological examination. The samples in this study were women with adenomyosis and women with no adenomyosis who are categorized into four criteria as follows: 1) Age (20-35 years old and >35 years old), 2) Education (High and Low), 3) Parity (Primiparous, Multiparous and Infertile) and 4) Menstrual Cycle (Regular and Irregular).

Preliminary research (collecting data): In collecting data, this study used three tools as follows: 1) Questionnaire, 2) a measurement of interleukin 10 levels with ELISA technique, and (3) Histopathological examination to diagnose adenomyosis. This study thought that it was important to firstly identify and determine the characteristics of the samples and the results of IL-10 level measurement between the adenomyosis women and non-adenomyosis women by using Chi-square test and Mann-Whitney test. After describing and determining the characteristics of the samples and the results of IL-10 level, this study attempted to determine and investigate the correlation of adenomyosis with IL-10 levels by using Spearman correlation test in SPSS software.

Data analysis: The comparative analytic research has been carried out using a nested case control research design to find out the comparison of interleukin 10 (IL-10) level in women with adenomyosis and without adenomyosis.

RESULTS

Research sample characteristics: There are four criteria in the research samples. This study has done with its first identification towards the characteristics of the research samples and the results of IL-10 level by using Chi-square test. It can be seen from the Table 1 as follow:

From respondents aged 20-35 years, 22 respondents (59.5%) did not experience adenomyosis, while respondents who were more than 35 years old; 22 respondents (59.5%) of whom experienced adenomyosis. Chi square test results obtained p-value = 0.104 ($p > 0.05$). It meant that there was no difference in age group of the two groups. The respondents who had higher education level did not experience adenomyosis as many as 31 respondents (83.8%), while respondents who had a low level of education experienced more adenomyosis as 11 respondents (29.7%). Chi-square test results obtained p-value = 0.167 ($p > 0.05$). It meant that there was no difference in the level of education between the two groups.

There were 11 respondents (29.7%) with more primiparous parity did not experience adenomyosis, and 23 respondents (62.2%) who had more multiparous parity did not experience adenomyosis, while infertile respondents experienced more adenomyosis as 7 respondents (18.9%). Chi square test results obtained p value = 0.351 ($p > 0.05$). It meant that there was no difference in parity between the two groups. The respondents who had regular menstrual cycles were the same among those who experienced adenomyosis and no adenomyosis; each of them were 26 respondents (70.3%), while respondents who had irregular menstrual cycle, cycles were also the same among those who experienced

adenomyosis with no adenomyosis as 11 respondents (29.7%). Chi-square test results obtained p-value = 1,000 ($p > 0.05$). It meant that there was no difference in menstrual cycles between the two groups.

Average of IL-10 levels in the adenomyosis group and control group:

The average of interleukin-10 level for respondents who experienced adenomyosis was 930.43 while those without adenomyosis were 662.02. Mann-Whitney test and no adenomyosis (Table 2). Results revealed p-value = 0.001 ($p < 0.05$). This meant that there is a difference in interleukin-10 levels between adenomyosis.

Correlation between IL-10 levels and adenomyosis:

The result of Spearman correlation test showed that there was a correlation between IL-10 levels and adenomyosis ($p < 0.05$). The value of $r = 0.381$ meant that the strength of the relationship is weak (Table 3).

The correlation between IL-10 levels and adenomyosis:

The result of Spearman correlation test showed that there was a correlation between IL-10 levels and adenomyosis ($p < 0.05$). The value of $r = 0.381$ meant that the strength of the relationship is weak (Table 3).

Correlation between IL-10 levels and tumor size :

The correlation test results shown that there was a correlation between interleukin-10 levels and tumor size ($p < 0.05$). The value of $r = 0.569$ meant the strength of the relationship is moderate. It was shown in Table 4 that higher level of IL-10 correlated to the greater size of the tumor.

Table 1: Distribution of research sample characteristics using chi-square test

Respondent's Characteristics	Groups						p-value
	Adenomyosis		Control		Number		
	Number	Percentage	Number	Percentage	Number	Percentage	
Age							
20-35 years	15	40.5	22	59.9	37	50	0.104
>35 years	22	59.5	15	40.5	37	50	
Education							
High	26	70.3	31	83.8	57	77.0	0.167
Low	11	29.7	6	16.2	17	23.0	
Parity							
Primiparous	8	21.6	11	29.7	19	25.7	0.351
Multiparous	22	59.5	23	62.2	45	60.8	
Infertile	7	18.9	3	8.1	10	13.5	
Menstrual Cycle							
Regular	26	70.3	26	70.3	52	70.3	1.000
Irregular	11	29.7	11	29.7	22	29.7	

Table 2: Mean of IL-10 levels in the adenomyosis group and control group using mann-whitney test

Groups	IL-10	
	Mean±SD	p-value
Adenomyosis	930.43±970.04	0.001
Without adenomyosis	662.02±918.93	-

Table 3: Correlation between IL-10 levels and adenomyosis using spearman correlation test

Groups	IL-10		
	Mean±SD	r-value	p-value
Adenomyosis	930.43±970.04	-	0.01
Without adenomyosis	662.02±918.93	0.381	-

Table 4: Correlation between IL-10 levels and tumor size using spearman correlation test

parameters	Mean±SD	r-value	p-value
IL-10 level	930.43±970.04	-	<0.001
Tumor size	10.81±4.02	0.569	-

DISCUSSION

This study showed that the levels of interleukin 10 patients with adenomyosis were higher than women who did not suffer from adenomyosis. It was also found a weak correlation between levels of IL-10 with adenomyosis and moderate correlation between levels of IL-10 with adenomyosis size. These findings are showed contradiction with a research by Harada *et al.*¹² and Vannuccini *et al.*¹³ that there is a normal correlation between levels of IL-10 with adenomyosis and moderate correlation between levels of IL-10 with adenomyosis. The findings of this study are consistent with research conducted by Wang *et al.*⁷ that there was an increase in the level of Interleukin-10 in ectopic and eutopic endometrial patients with adenomyosis. Interleukin 10 expression contributed to maintaining immunosuppressive conditions. It can explained the presence of persistent ectopic focus in the peritoneal cavity or in the myometrium without the elimination of the immune system in women with adenomyosis or endometriosis⁷.

Research conducted by Qin *et al.*³ showed an increase in the expression of IL-10 and IL-10R1 in endometrial eutopic and ectopic patients with adenomyosis. This allowed eutopic endometrial cells to escape the body's immunological surveillance, so that it can form adenomyosis. IL-10 can triggered biological effects such as creating an immunosuppressive effect that can benefit tumor growth. In addition, IL-10 induced HLA-G as one of the components needed by cells to defend themselves from immunological reactions. In this case, it can be used by tumor cells to avoid host cell immune surveillance. In addition, IL-10 also, inhibited

cytokine secretion from Th1 cells and reduce activation of peritoneal T-cells. Thus, it can be assumed that the presence of elevated IL-10 levels can lead to tolerance of the endometrial ectopic and eutopic immune responses. Therefore, before the endometrium infiltrates the myometrium, endometrial eutopic first expresses IL-10 to increase the success of the endometrium in infiltrating the myometrium thus it did not get an immune response to the myometrial anti-inflammatory system components⁷.

The same results were also shown in a study conducted by Zhihong *et al.*¹⁴ which found an increase in macrophage, IL-6, IL-10 and MCP1 RNA expression in endometrial eutopics with adenomyosis compared to normal endometrium. A research conducted by Fan *et al.*¹⁵ Also reported an increase in serum IL-10 levels in adenomyosis patients. Besides IL-10, it was also found an increase in other anti-inflammatory cytokines, IL-37, while IL-17A and TNF level, such as pro-inflammatory cytokines were decreased. In this study, there was a correlation between IL-10 levels and the size of adenomyosis. The same correlation was also stated by Othman *et al.*¹⁶ in hepatocellular carcinoma. Immunosuppressive effects of IL-10 played an important role in neoplastic processes by suppressing the activation of macrophages and the production of interferon gamma which causes tumor cells to escape immune surveillance and the potential for metastasis. IL-10 which binds to its receptors in tumor cells can prevent cell death programs and increase cell proliferation.

Other studies reported the increased expression of IL-10 in adenomyosis tissue. Whereas in this study, similar results were observed. Therefore, it can be analyzed that increased expression of IL-10 in the tissue is likely to be associated with an increase in serum levels and it is similar to the finding of research by Trifunovic *et al.*¹⁷ and Lauridsen *et al.*¹⁸ In this study, it was not possible to rule out the presence of degree I and II endometriosis that can accompany adenomyosis, so that the obtained value of IL-10 levels may still have a bias whether purely caused by adenomyosis itself or due to the presence of endometriosis degrees I and II. This is the weakness and limitation of this study. Moreover present investigation suggested that further research are required to compare the levels of pro-inflammatory and anti-inflammatory cytokines in adenomyosis.

CONCLUSION

This study concluded that there was increased levels of IL-10 in adenomyosis patients compared with no adenomyosis. IL-10 levels correlated weakly with the incidence

of adenomyosis and were correlated moderately to the size of adenomyosis. Authors suggested that further studies should be carried out to compare IL-10 levels in serum with IL-10 expression in tissues so that it can determine whether there is a correlation between IL-10 levels in serum and IL-10 expression in tissues.

SIGNIFICANCE STATEMENT

This study discovered the levels of IL-10 in women with adenomyosis were higher compared to the women without adenomyosis ($p = 0.001$). IL-10 levels have a weak correlation with the incidence of adenomyosis and medium correlation with the size of adenomyosis. It can be beneficial for the development of woman research and woman health care service. This study will help the researchers to uncover the critical areas of adenomyosis that many researchers were not able to explore. Thus a new model of analysis on the correlation of IL-10 between women with adenomyosis and without adenomyosis may be arrived at.

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