

Research Article

The Level of Ca-125 in Pre- and Post-operative of Endometriosis

Kadar Ca-125 pada sebelum dan setelah Operasi Endometriosis

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Abstract

Objective: To determine the Ca-125 level in pre- and post-operative of endometriosis and its correlation to endometriosis stage and severity of dysmenorrhea.

Method: This was a cross-sectional study design conducted at Dr. Wahidin Sudirohusodo dan some affiliated hospitals. We took the patients undergoing laparoscopy or laparotomy consecutively.

Result: The mean value of preoperative Ca-125 level in stage I-II was 21.53 (SD 12.64) IU/ml vs 72.52 (SD 8.52) IU/ml in stage III-IV. The mean value of postoperative Ca-125 level was 14.82 (SD 10.00) IU/ml (stage I-II) vs 61.03 (SD 8.43) IU/ml (stage III-IV); they were significantly different ($p < 0.001$). There was a significant correlation between Ca-125 level and the stage of endometriosis ($r = 0.43$ and 0.52 ; $p = 0.005$). We observed mild to severe dysmenorrhea for stage I-II; while, patients had moderate to severe dysmenorrhea in stage III-IV ($p < 0.001$) and both of them showed a significant correlation ($r = 0.318$ and 0.537 ; $p < 0.05$). The Ca-125 level in stage I-II endometriosis was lower than stage III-IV.

Conclusion: Level of Ca-125 will decrease after endometriosis surgery. There is a strong correlation between preoperative level of Ca-125 and endometriosis stage. The severity of dysmenorrhea has the correlation to the stage of endometriosis.

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Keywords: Ca-125, dysmenorrhea, endometriosis

Abstrak

Tujuan: Mengetahui kadar Ca-125 sebelum dan setelah operasi endometriosis dan hubungannya dengan stadium endometriosis dan derajat dismenorea.

Metode: Penelitian dilakukan di BLU RS Dr. Wahidin Sudirohusodo dan rumah sakit afiliasinya dengan menggunakan desain potong lintang pada pasien laparotomi/laparotomi.

Hasil: Rerata kadar Ca-125 preoperatif pada endometriosis stadium I-II adalah 21,53 (SB 12,64) IU/ml vs 72,52 (SB 8,52) IU/ml pada stadium III-IV. Rerata kadar Ca-125 pascaoperasi adalah 14,82 (SB 10,00) IU/ml (stadium I-II) vs 61,03 (SB 8,43) IU/ml (stadium III-IV), terdapat perbedaan bermakna kadar Ca-125 baik pre- maupun pascaoperasi ($p < 0,001$) dan menunjukkan korelasi bermakna antara kadar Ca-125 preoperatif dan stadium endometriosis ($r = 0,431$ dan $0,524$; $p = 0,005$). Dismenorea derajat ringan sampai berat terdapat pada stadium I-II sedangkan derajat sedang sampai berat pada stadium III-IV ($p < 0,001$) dan keduanya menunjukkan korelasi bermakna ($r = 0,318$ dan $0,537$; $p < 0,05$). Kadar Ca-125 endometriosis stadium I-II lebih rendah dibandingkan stadium III-IV.

Kesimpulan: Kadar Ca-125 menurun pascaoperatif. Terdapat hubungan antara kadar Ca-125 preoperatif dengan stadium endometriosis. Derajat dismenorea berkorelasi dengan stadium endometriosis.

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Kata kunci: Ca-125, dismenorea, endometriosis

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INTRODUCTION

Endometriosis occurs around 10-15% of reproductive age women. Endometriosis causes a lot of problem, which one of them is infertility. Many studies have proved this relationship; however, the causal relationship between both of them are still controversial.¹

Actually, the prevalence of endometriosis is unknown. The definitive diagnosis of endometriosis can be performed through laparoscopy or surgery; meanwhile, it will not do to the women without specific symptoms of physical examination suggesting to the diseases. Therefore, there are various indications for surgical treatment for endometriosis.^{2,3}

Apart from the infertility problem faced by endometriosis, the pain of endometriosis impacts to quality of life which can be assessed through Health-Related Quality of Life (HRQOL). The pelvic pain is the major causes of productivity loss in reproductive age women. Therefore, we as the health professional should put more awareness to the disease in primary health center by early diagnostic and prompt treatment to improve the productivity of women.⁴

A non-invasive diagnostic test of endometriosis is required to prevent the delay between onset of symptoms and diagnosis of disease. The diagnosis of endometriosis is difficult to determine due to the variation of clinical symptoms. We should consider

endometriosis if patients are complaint about the dysmenorrhea. Dysmenorrhea as a common gynecologic disorder in women with endometriosis at childbearing age is the sensation of pain during menstruation. It usually makes cramping and is located on the lower abdomen.^{3,5} Dysmenorrhea affects health and quality of life. Many studies conducted on different populations reported the prevalence was ranged between 20% and 94%.⁵⁻⁷

Currently, laparoscopy is the gold standard to confirm diagnosis and treatment of endometriosis. Unfortunately, this procedure has not been performed in most hospitals in Indonesia. Therefore, a simple modality prior to surgery is required to diagnose the endometriosis.

The tumor marker of Ca-125 is the most extensively investigated and used as the peripheral biomarker of endometriosis. The Ca-125 is produced by endometrial and mesothelial cells and released into circulation via the endothelial lining of capillaries in response to inflammation. However, Ca-125 level in the peripheral lacks diagnostic power as a single biomarker of endometriosis.⁸ The level of Ca-125 usually elevates in endometriosis, especially in moderate and severe stage of endometriosis. Mol, et al. through their study showed the routine examination of serum Ca-125 in infertile patients could identify a subgroup of patients who are more likely to get benefit from early laparoscopy though, Ca-125 had limited diagnostic performance.⁹ Although its limited diagnostic performance, Ca-125 was still examined prior to surgery and it was used as the monitoring tool of the endometriosis development after treatment in patients with epithelial ovarian cancer, endometriosis, endometrial cancer, and also cervical adenocarcinoma.¹⁰

Therefore, this study aims to determine Ca-125 level pre- and post surgery. Apart from that, we would like to know the correlation to the stage of endometriosis and severity of dysmenorrhea.

METHODS

This cross-sectional study was conducted between May and September 2015 in Dr. Wahidin Sudirohusodo and some affiliated hospitals. The samples were taken from women at reproductive age who had been diagnosed with endometriosis and dysmenorrhea. They would perform the laparoscopy or laparotomy. Then, we collected the blood sam-

ples from patients pre- and postoperative to measure the Ca-125 level at Prodia Diagnostic Laboratory Makassar. The endometriosis stage was determined by the American Society of Reproductive Medicine (ASRM) criteria at the time of surgery.¹¹ The severity of dysmenorrhea associated with endometriosis was measured with Numerical Rating Scale (NRS). Data were analyzed using Mann-Whitney test, Fisher exact test, Wilcoxon and Spearman correlation test.

RESULTS

There were sixty subjects confirmed endometriosis during surgical whereas nineteen subjects had stage I-II and forty-one subjects had stage III-IV. There were no statistically different in age, marital status, infertility, duration of marriage, parity and contraception between stages of the disease (Table 1).

Table 1. Subject Characteristics

| Characteristics | Endometriosis Stages n (%) | | p |
|-----------------------------|-------------------------------|--------------------|-------|
| | I-II (n = 19) | III-IV (n = 41) | |
| Age (year) | 31.2 | 32.7 | 0.271 |
| Marital Status | | | |
| Not married | 5(26.3) | 7(17.1) | 0.493 |
| Married | 14(73.7) | 34(82.9) | |
| Infertility | | | |
| Primary | 12(85.7) | 23(67.6) | 0.292 |
| Secondary | 2(14.3) | 11(32.4) | |
| Duration of Marriage | | | |
| <5 years | 12(85.7) | 22(64.7) | 0.181 |
| ≥5 years | 2(14.3) | 12(35.3) | |
| Parity | | | |
| 0 | 7(77.8) | 10(47.6) | 0.273 |
| <3 | 2(22.2) | 9(42.9) | |
| ≥3 | 0 | 2(9.5) | |
| Contraception | | | |
| Non user | 12(85.7) | 27(79.4) | 0.646 |
| OC (hormonal) | 2(14.3) | 5(14.7) | |
| IUD (non-hormonal) | | 2(5.9) | |

The mean level of Ca-125 preoperative for stage I-II endometriosis was 21.52 (SD 12.64) IU/ml and 14.82 (SD 10.0) IU/ml for postoperative. In stage

III-IV, preoperative level of Ca-125 was 72.52 (SD 8.52) IU/ml and 61.03 (SD 8.43) IU/ml after the surgical. Actually, the Ca-125 level preoperative for stage I-II endometriosis was higher than stage III-IV. There were significant differences for all of endometriosis stages on Ca-125 level in preoperative and postoperative ($p < 0.001$). The stage I-II endometriosis was strongly correlated ($r = 0.524$) with preoperative level of Ca-125; while, there was moderate correlation in stage III-IV ($r = 0.431$). There was significant correlation between Ca-125 level and all of the endometriosis stages ($p < 0.05$) (Table 2).

Patients in stage I-II experiencing mild, moderate, and severe pain of dysmenorrhea was 31.6%, 57.9%, and 2%; respectively. Meanwhile, patients with stage III-IV experienced moderate (51.2%) and severe (48.8%) pain of dysmenorrhea. There were significantly different ($p < 0.001$) between severity of dysmenorrhea and endometriosis. The severity of dysmenorrhea had strong correlation with stage I-II ($r = 0.537$; $p = 0.018$) compared with stage III-IV (Table 3).

DISCUSSION

The results showed a significant difference between Ca-125 level and all of the stages in endometriosis. This study also showed a correlation between the degree of dysmenorrhea and endometriosis stage.

The mean age at diagnosis of endometriosis was between 25 and 35 years old.³ This study found similar average age of diagnosis for endometriosis

where the mean age for stage I-II was 31.2 years old and 32.7 years old for stage III-IV. Actually, our subjects characteristic were alike between groups because they showed the normal distribution ($p > 0.05$). Increased age in women affects fecundity and lower fertility. Subfertility due to endometriosis can occur through two mechanisms namely the distortion of adnexal anatomy that inhibits or prevents ovum capture after ovulation and excess of prostaglandins, metalloproteinases, cytokines and chemokines which is resulted into chronic inflammation. This chronic inflammation will impair the ovarian, tubal or endometrial function leading to the disorders of folliculo genesis, fertilization, or implantation. The first mechanism provides a logical explanation for infertility in women with advanced stage of endometriosis. The second mechanism is valid for women with mild stage of endometriosis; nevertheless, the cause of infertility from mild to moderate endometriosis is still controversial.^{3,12}

The use of contraception both hormonal and non-hormonal was not significantly associated with all of the stages in endometriosis due to small sample size. Chapron, et al. study showed that there was no relationship between the new user of contraceptive pills and endometriosis. This study also indicated that the history of oral contraceptive user for treating severe primary dysmenorrhea was associated with endometriosis, especially in the type of deep infiltrating endometriosis. However, this did not mean that the use of oral contraception would increase the risk of developing endometriosis. The history of contraceptive pill user

Table 2. Pre- and Post-operative of Ca-125 Level

| Endometriosis Stages | Ca-125 Level (mean (SD) IU/ml) | | <i>p</i> | Ca-125 Preoperative | |
|----------------------|--------------------------------|---------------|----------|---------------------|----------|
| | Preoperative | Postoperative | | <i>r</i> | <i>p</i> |
| I-II | 21.53 (12.64) | 14.82 (10.00) | <0.001 | 0.524 | 0.021 |
| III-IV | 72.52 (8.52) | 61.03 (8.43) | <0.001 | 0.431 | 0.005 |

Table 3. Dysmenorrhea and Endometriosis Stages

| Severity of Dysmenorrhea | Endometriosis Stages (%) | | <i>p</i> | Stage I-II | | Stage III-IV | |
|--------------------------|--------------------------|---------------|----------|------------|----------|--------------|----------|
| | I-II (n=19) | III-IV (n=41) | | <i>r</i> | <i>p</i> | <i>r</i> | <i>p</i> |
| Mild | 6 (31.6) | 0 | | | | | |
| Moderate | 11 (57.9) | 21 (51.2) | 0.000 | 0.537 | 0.018 | 0.318 | 0.043 |
| Severe | 2 (10.5) | 20 (48.8) | | | | | |

could use as the marker for women with endometriosis and deep infiltrating endometriosis.¹³ A study by Vercellini, et al also reported that the incidence of endometriosis was lower in new user of oral contraceptive pills than old user.¹⁴

Preoperative level of Ca-125 in stage I-II was lower than stage III-IV. The Ca-125 level in endometriosis was varied on the period of study, although the Ca-125 level increased at advanced stage of endometriosis compared with stage I-II. Barbieri, et al. in their study measured serum Ca-125 level preoperative in 147 patients performed diagnostic laparoscopy or laparotomy. The result pointed out that the serum Ca-125 level increased in stage III or IV endometriosis than in control group. Around 54% of patients with stage III or IV endometriosis and 0% of control group had the level of Ca-125 more than 35 IU/ml.¹⁵ The result was consistent to the previous studies that the level of Ca-125 was higher in advanced stage of endometriosis which the value was more than 35 IU/ml.

Preoperative abdominal preparation showed that women with high level of Ca-125 more than 65 IU/ml (the normal range was under 35 IU/ml) was more likely to have dense omental adhesion, ruptured endometrium as or cul-de-sac obliteration.³ Another study on 44 women who underwent laparoscopy to confirm the diagnosis of endometriosis showed that the level of Ca-125 was 33.98 IU/ml vs 9.3 IU/ml in control.¹⁶

Correlation test result showed there was a strong correlation between elevated level of Ca-125 and the stage of endometriosis. The Ca-125 level increases in women with advanced stage, especially during early pregnancy and normal menstruation in women as well as acute PID or leiomyomata.³ Therefore, the time of blood sampling for measuring Ca-125 level during menstrual cycle affects the result because the high level of Ca-125 occurs during menstruation and immediately after menstruation.¹⁷ Similar finding result concerning higher Ca-125 level during the menstrual phase was presented by Abrao, et al. They stated that the level of Ca-125 marker reached the highest value during the menstrual phase between the first and third day compared with the luteal phase. Increased marker of Ca-125 in women with endometriosis occurs because the level of Ca-125 is higher in ectopic endometrium compared with endometrium.¹⁸ The increase in Ca-125 can

also happen because of the inflammatory reaction altering the endothelial permeability, thereby it allows the Ca-125 enter into circulation.¹⁵

Another factor that also affects the level of serum Ca-125 is the age. However, several studies reported conflicting results; some studies reported that the level of Ca-125 decreased as increasing the age; while, another study showed the contrary result.¹⁹ The effect of age on level of Ca-125 for all stages in this study was not analyzed.

Laparoscopy for endometriosis is used to remove lesions, adhesion, and cysts through excision, electrocautery, laser vaporization, and repair of pelvic anatomy. Apart from that, it is the preferred method for the treatment of infertile women with mild-moderate endometriosis. Uterosacral nerve ablation and pre-sacral neurectomy may also be considered to relieve the chronic pelvic pain.²⁰

The assessment of the dysmenorrhea severity showed that mild to severe dysmenorrhea was occurred in stage I-II of endometriosis; while, moderate to severe dysmenorrhea was happened in stage III-IV. This suggested that the severity of dysmenorrhea increased as the increasing stage of the disease. In a prospective study by Chapron, et al showed that the assessment of the dysmenorrhea severity was similar in women with superficial endometriosis, cystic ovarian endometriosis, and deep infiltrating endometriosis where the assessment was measured using a visual analog scale. Besides, the severity of pain was higher in women without endometriotic lesion.²¹ The relationship between the stages of endometriosis based on the Revised American Society Fertility was inconsistent to the dysmenorrhea. Several studies reported a correlation between the stage of endometriosis and dysmenorrhea.^{22,23} Other studies indicated there was no correlation.^{24,25} Study by Chapron, et al. showed a linear relationship between the stage of endometriosis and the severity of endometriosis through severe adnexal adhesion and obliteration of the Douglas pouch. It was strongly correlated to the degree of visceral adhesion infiltration or deep infiltrating endometriosis implant.²¹ This explanation supported the result in this study that moderate to severe dysmenorrhea was occurred in stage III-IV; while, mild to severe dysmenorrhea in stage I-II was due to endometriotic implant superficial infiltration.

The pain due to mild endometriosis was more likely to be associated with the focal inflammation

from cyclic bleeding surrounding the peritoneal implant or the action of inflammatory cytokines by a large number of macrophages and other immune cells in the peritoneal fluid of women with endometriosis. Cytokines are produced by most cell types including endometriotic tissue which has the role in the pathogenesis of endometriosis and infertility.²⁶ Severe dysmenorrhea and dyspareunia are common symptoms of endometriosis. The intensity of pain because of deeply infiltrating endometriosis is correlated with the depth of penetration and proximity or direct invasion of the nervous system. However, the severity of endometriosis does not have correlation with the number and severity of dysmenorrhea. Meanwhile, women with advanced stage of endometriosis may experience mild or without dysmenorrhea as well as the dysmenorrhea in women with mild or moderate endometriosis.³

CONCLUSION

The Ca-125 level is decreased after surgical. There is a strong correlation between preoperative level of Ca-125 and endometriosis stage. The severity of dysmenorrhea has the correlation to the stage of endometriosis. The examination of preoperative level of Ca-125 and severity of dysmenorrhea is able to identify the possibility of endometriosis although it is not recommended to determine the stage of endometriosis.

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