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EDITORIAL

Should All Patients With Endometriosis Undergo Surgery?

Tono Djuwantono

Not every endometriotic patients should undergo surgery; the treatment of this condition should be adjusted to the needs and age of the patients. Medical treatment should be administered to teenagers and unmarried patients, and it could be given to reduce pain and prevent recurrence. However, medical treatment cannot improve fertility problems, particularly to those who expect pregnancy.¹

Surgical therapy is suitable for those expecting pregnancy. It not only reduces pain but also improves the microenvironment of adnexa and peritoneal, thereby increasing fertility.^{1,2} Based on our results, those with endometriosis who underwent laparoscopic surgery had the rate spontaneous pregnancy of 46.3% within a year after surgery.³ However, it should be noted that the recurrence rate increased within a year in the absence of pregnancy.^{1,4} Careful monitoring should be performed during the first year after surgery to increase the potency of fertility, and providing adjuvant hormonal therapy when necessary to reduce the risk of recurrence.^{4,5} Medical treatment should be given for those who do not expect pregnancy to prevent recurrence.⁶ However, if pregnancy is expected, assisted reproductive technology (ART) could be given immediately according to the patient problems. Any individual or clinic dealing with endometriosis surgery should establish risk management for recurrence since recurrence may worsen the fertility prognosis. The combination of surgical and adjuvant hormonal therapy is recommended before ART for endometriosis patients with AFS III/IV accompanied by complications such as hydrosalpinx, adhesion, and adenomyosis in order to improve the outcome of IVF.⁷ Any individual or clinic treating endometriosis should expand the paradigm "performed endometriosis surgery, dare to prevent recurrence" and "performed endometriosis surgery, dare to increase reproductive potential".

References

1. Kaur KK, Allahbadia G. An Update on Pathophysiology and Medical Management of Endometriosis. *Advances Reprod Scienc*. 2016; 4: 53-73.
2. Singh SS, Suen MW. Surgery for endometriosis: beyond medical therapies. *Fertil Steril*. 2017; 107(3): 549-54.
3. Tjandraprawira KD, Djuwantono T. Postlaparoscopic GnRH agonist Therapy does not Improve Spontaneous Conception Rates of Women with Endometriosis. *Indones J Obstet Gynecol*. 2017; 5(2): 87-93.
4. Kikuchi I, Takeuchi H, Kitade M, Shimanuki H, Kumakiri J, Kinoshita K. Recurrence rate of endometriomas following a laparoscopic cystectomy. *Acta Obstet Gynecol Scandinavica*. 2006; 85(9): 1120-4.
5. Muzii L, Marana R, Caruana P, Catalano GF, Margutti F, Panici PB. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. *Am J Obstet Gynecol*. 2000; 183(3): 588-92.
6. Ota Y, Andou M, Yanai S, Nakajima S, Fukuda M, Takano M, dkk. Long-term administration of dienogest reduces recurrence after excision of endometrioma. *J Endomet Pelvic Pain Disorders*. 2015; 7(2): 63-7.
7. Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BW. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. *The Cochrane database of systematic reviews*. 2010(1): CD002125.

Research Article

The Role of Progesterone-Induced Blocking Factor in Threatened Abortion

Peran Progesterone-Induced Blocking Factor pada Abortus Iminens

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Abstract

Objective: To determine the role of progesterone-induced blocking factor (PIBF) in women with threatened abortion.

Methods: This was a cross-sectional study. The blood serum of two groups, the first one was women with normal gestation of ≤ 20 weeks, and the second one was those with imminent abortion in Prof. Dr. R.D. Kandou Hospital, and Subcenter Hospital in Manado, was collected. Samples were processed with PIBF ELISA-kit.

Results: PIBF serum value of women in normal gestation ≤ 20 weeks is (47.153 ± 23.830) ng/ml and threatened abortion is (11.540 ± 4.892) ng/ml, with p value = 0.000.

Conclusion: PIBF serum value of women with threatened abortion is significantly lower compared to women of normal gestation ≤ 20 weeks. This study showed that PIBF has an important role in maintaining pregnancy and can be used as a biologic marker of a pathologic process in pregnancy.

[Indones J Obstet Gynecol 2017; 5-4: 193-198]

Keywords: early pregnancy, pregnancy immunology, progesterone-induced blocking factor, threatened abortion

Abstrak

Tujuan: Mengetahui kadar PIBF serum perempuan hamil usia kehamilan normal ≤ 20 minggu dan abortus iminens sehingga dapat menambah pemahaman mengenai PIBF sebagai petanda biologis patologi kehamilan, dan dalam upaya terapi rasional pasien dengan abortus iminens.

Metode: Penelitian analitik komparatif potong lintang terhadap 32 pasien yang dibagi menjadi 2 kelompok kehamilan normal ≤ 20 minggu, dan abortus iminens di RSUP Prof Dr. R.D. Kandou, beserta RS Jejaring di wilayah Manado, dilakukan pengambilan sampel serum. Sampel dilakukan pemeriksaan kadar PIBF dengan ELISA-kit. Data diproses menggunakan program SPSS versi 22.0.

Hasil: Kadar PIBF serum perempuan hamil usia kehamilan ≤ 20 minggu normal $(47,153 \pm 23,830)$ ng/ml dan abortus iminens $(11,540 \pm 4,892)$ ng/ml ($p=0,000$).

Kesimpulan: Kadar PIBF serum perempuan hamil dengan abortus iminens lebih rendah secara bermakna dibandingkan kadar PIBF serum perempuan hamil usia kehamilan ≤ 20 minggu normal. Hasil ini menunjukkan bahwa PIBF berperan dalam mempertahankan kehamilan dan dapat digunakan sebagai sarana petanda adanya proses patologi dalam suatu kehamilan.

[Maj Obstet Ginekolog Indones 2017; 5-4: 193-198]

Kata kunci: abortus iminens, imunologi kehamilan, kehamilan muda, progesterone-induced blocking factor

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INTRODUCTION

Fetus is a semi-allogenic tissue which relies inside the body of a woman whose immune-competent of producing rejection immune response, therefore modulation of maternal immune response is required to maintain pregnancy.¹

During pregnancy, many complications may occur, which may lead to early termination of pregnancy. Abortion is defined as the loss of pregnancy either spontaneous or induction before being viable (gestational age < 20 weeks). Abortion can result in physical and emotional disturbance. The incidence of spontaneous abortion is between 15-20% from all pregnancy. Predisposing factors

of spontaneous abortion include genetic factors, anatomy, endocrine, immune, infection, thrombophilia, and idiopathic.²⁻⁴

Maternal immune response to fetus has an important role as a predisposing factor in spontaneous abortion, and it is often unexplainable. The current hypothesis is the presence of multiple factors which may affect at systemic, and local *in utero*, determine to modulate immune response into decreasing inflammation response of trophoblasts. Factors involved in this process are hormones, particularly progesterone, embryonic hormones, and Natural Killer cells (NK cells).^{1,2}

In daily clinical practice, progesterone supplement is often used as a supportive therapy for pregnant women who are diagnosed with threatened abortion. Progesterone has an important role in modulating immune response in early trimester pregnancy through modulating pro-inflammatory and anti-inflammatory cytokines from conceptus, resulting in the continuation or termination of pregnancy.

With the influence of progesterone, lymphocyte releases protein called progesterone-induced blocking factor (PIBF), which mediates the modulation of immune response and the anti-abortion effect of progesterone. This process also gives positive feedback, there by increasing the amount of progesterone receptors in the activated lymphocyte in the placental cells and CD8⁺ cells. In return the amount of PIBF will increase along with the gestational age from week 6 to 36, and after 41 weeks, PIBF will decrease considerably and induce the parturition. PIBF also inhibits peripheral NK cells activity. The biological effects of PIBF as mentioned above indicates that PIBF has a role in maintaining pregnancy. Therefore, PIBF value in the body liquid can predict the prognosis of pregnancy.⁵

A Cochrane review in 2013 demonstrated that there was no significant difference between progesterone supplementation and placebo in maintaining pregnancy. Nevertheless, Check JH mentioned that although progesterone deficiency occurs in one third of pregnancy, progesterone supplementation to improve PIBF value still has a role in decreasing 33% spontaneous abortion.⁶⁻⁸

Considering the impact of abortion in the physical and emotional aspects of the patient's, and to

learn further the role of immune-endocrine (PIBF) in affecting the prognosis of pregnancy, we are interested in doing this study.

METHODS

This was a cross-sectional study. Subjects were pregnant women with gestational age of ≤ 20 weeks at Prof. Dr. R.D. Kandou Hospital, and subcenter hospital in Manado during the period of October 2015 to February 2016. Samples were collected by consecutive sampling. Total population consisted of 32 patients, divided into two groups: 16 with normal pregnancies, and 16 threatened abortions that matched the inclusion and exclusion criteria.

Inclusion criteria were single pregnant women with less than 20 weeks of gestation confirmed by ultrasound. Exclusion criteria were pregnant women with history of recurrent pregnancy loss, those who were currently receiving progesterone therapy, and fetal death or blighted ovum.

Blood samples from subjects were collected, and examined with PIBF ELISA-kit in the Prokita Laboratory Manado.

Data were analyzed using T-test to investigate the significance of PIBF value in the normal early pregnancy and threatened abortion. Data were processed using Statistical Product and Service Solutions (SPSS) 22.0 for Windows.

RESULT

Subject Characteristics

Table 1. Maternal Age Frequency Distribution

		Maternal age (year)			Total
		<20	20-34	≥ 35	
Groups	Normal pregnancy	1	10	5	16
	Threatened abortion	1	12	3	16
Total		2	22	8	32

Interpretation: most maternal age of subjects are around 20-34 years old.

Table 2. Educational Status Frequency Distribution

		Educational status				Total
		Elementary	Junior high school	High school	Bachelor	
Groups	Normal pregnancy	2	1	9	4	16
	Threatened abortion	4	6	5	1	16
Total		6	7	14	5	32

Interpretation: most educational status of subjects are at high school.

Table 3. Gravidity Status Frequency Distribution

		Gravidity status		Total
		First	Multi	
Groups	Normal pregnancy	4	12	16
	Threatened abortion	6	10	16
Total		10	22	32

Interpretation: most gravidity status of subjects are multiple.

Table 4. Gestational Age Frequency Distribution

		Gestational age (weeks)				Total
		4-8	9-12	13-16	17-20	
Groups	Normal pregnancy	7	6	3	-	16
	Threatened abortion	1	4	2	9	16
Total		8	10	5	9	32

Interpretation: most gestational age of subjects are around 9-12 weeks.

PIBF Serum Value

Our study showed that PIBF serum value of threatened abortion was lower than normal pregnancy in all groups of gestational age; with details as follow: the first group of 4-8 weeks of gestation (16.114 vs 48.62 ng/ml); in the second group of 9-12 weeks of gestation (11.107 vs 41.909 ng/ml); in the third group of 13-16 weeks of gestation (7.372 vs 54.217 ng/ml); while in the last group of 17-20 weeks of gestation there was no subject in the normal pregnancy group to compare with the threatened abortion (12.151 ng/ml).

An overall calculation of our data showed a significant difference of PIBF serum value in normal pregnant women of ≤ 20 weeks and threatened abortion (47.153 vs 11.540 ng/ml; p value=0.000). Variable coefficient data showed that the variation of PIBF serum in both groups were above 10%, this stated that the PIBF serum were not homogenous.

DISCUSSION

Pregnancy immune-biology

Throughout history of human evolution, humankind has developed a mechanism to protect us from parasites and infections by detecting and destroying foreign organic materials that enter human's body. This mechanism is called the immune system.⁹

Fetus is a product of conception, which is a semi-allograft tissue. However, there is no rejection from the maternal immune system. This is due to the absence of MHC class I nor class II on the placental villous trophoblast, hence not inducing the NK cytotoxic activities.^{10,11}

Another factor protecting the fetus is the expression of FasL, a protein membrane type II that is commonly present in the immune-compromised tissue, such as testes, cornea, trophoblast (Houston, and O'Connell, 2004).¹²

Wegmann (1993) mentioned that Th1 (pro-inflammatory) and Th2 (anti-inflammatory) balance is the key of successful pregnancy. Whereas Th2 domination is required to protect feto-placental unit from the adaptive immune response, or non-specific inflammatory response.^{10,12}

Pro-inflammatory cytokines are critical in the early process of implantation to induce angiogenesis. Shortly after, it should be replaced by anti-inflammatory cytokines that shift the balance from Th1 to Th2 dominance. Szekeres-Bartho explained that TCD8⁺ cells in pregnant women expressed progesterone receptors since early pregnancy. Whereas, under progesterone influence, this lymphocyte cells express a mediator protein with molecular weight of 34kDa called PIBF (Progesterone-induced blocking factor).^{3,5,10,12,13}

through mediator PIBF. Depletion of progesterone production in pregnancy will initiate parturition. This is the main reason of progesterone supplementation therapy as luteal support to prevent abortion.¹⁵

PIBF as a research variable

As mentioned above, to have an immune-endocrine effect, progesterone needs protein mediator which is PIBF, which synthesized from the activated lymphocyte of T_γ/δ (CD8⁺).^{1-3,5,7} Progesterone supplementation is meant to improve PIBF value through its binding to progesterone receptors, and not to improve progesterone level.^{3-7,16}

The mechanisms of PIBF in maintaining pregnancy are through several pathways: by inhibiting peripheral NK cells cytotoxicity activity, by inducing Th2 cytokines domination and asymmetric antibody production (Ig G).¹⁷⁻²²

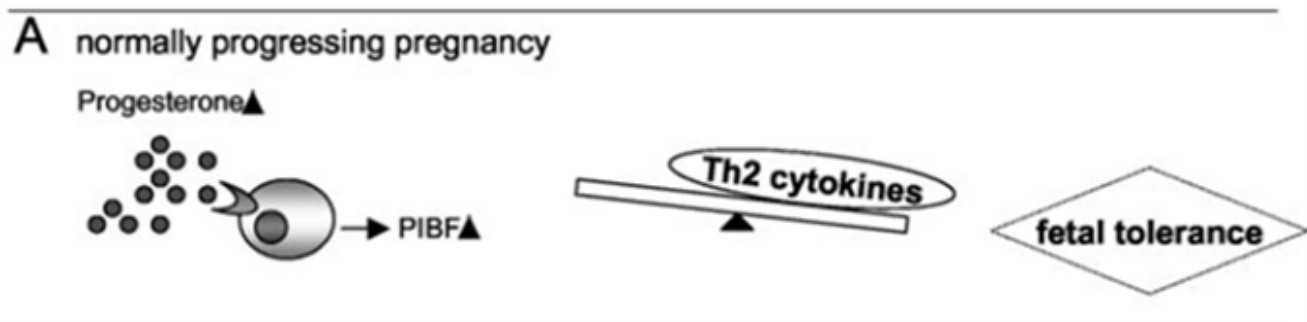


Figure 1. Normally Progressing Pregnancy. A schematic hypothesis of immune-endocrinology in pregnancy. In normal pregnancy, a sufficient concentration of progesterone leads to anti-inflammatory cytokines dominance (Th2), mediated by PIBF expression.¹³

The role of NK cells in pregnancy

NK cells dominated the leucocytes involved in the implantation process in early pregnancy. NK cells are classified as peripheral NK cells and uterine NK cells. In pregnancy, the amount of peripheral NK cells is depleted due to the minimal expression of CD16. This process is affected by the progesterone level.¹⁴ In contrast to peripheral NK cells, uterine NK cells are dominated in pregnancy. These NK cells have a small effect of cytotoxicity hence needed in pregnancy.¹⁴

Role of progesterone in pregnancy

Progesterone is the main hormone in maintaining pregnancy. It directly affects immune system or

PIBF expression required adequate, hence PIBF value will predict the outcome of pregnancy. This is according to the study done by B Polgar, etc which stated that PIBF in the body liquid will reflect the pathological condition of pregnancy.^{1,2,5,21,23}

PIBF value can be measured through urine or serum sample, this is due to the fact that the weight molecule is 34kDa, there by small enough to be excreted by renal of PIBF, this could be detected in the urine. PIBF value measurement through urine sample is often done because it is non invasive, yet 24 hours urine sample is needed to reduce the bias.^{1-3,5} Nonetheless, in this study we use serum sample, because it is considered the more consistent result due to a random one time sampling.

A study performed by Igor Hudic found difference between PIBF value in serum and urine, nonetheless it has the same predictive value where PIBF value in women with threatened abortion is lower than in normal pregnancy.² This is consistent with our study which found that PIBF serum value in threatened abortion is significantly lower than in normal pregnancy.

PIBF Serum Value

Previous studies have shown that PIBF has a role in maintaining pregnancy through immunological mechanism by modulating cytokine Th1/Th2 balance, suppressing cytotoxic and cytotoxic activity of NK cells, and by increasing asymmetric antibody production.^{1-3,5,7,13,19}

Our study showed that there were significant difference between PIBF serum value in normal pregnant women ≤ 20 weeks (47.153 ± 23.830) and threatened abortion (11.540 ± 4.892) (p value=0.000). This result is consistent with several studies which suggested that the presence of PIBF could be used as a biomarker of predicting the outcome of pregnancy or detecting pathological condition of pregnancy.^{1,2,5}

Our study showed that the coefficient variation is above 10%, meaning that PIBF value has a large variation. This might be due to the factors beyond the researcher control which cause the difference of progesterone production such as inflammatory process, different fetal development, infection factor, uterine stretch, or the maternal/fetal stress.²⁴ Similar studies performed before also have the same conclusion where mean PIBF in threatened abortion is lower significantly compared to normal pregnancy. Despite having different value, this may due to the different study methods, reagents, processing methods, wave length used in ELISA reader, samples amount, and gestational age used in the subjects.

This study showed that PIBF could be used as a biomarker of pathologic process in pregnancy. However, due to the cross-sectional study design, it is not possible to determine the cut-off point of PIBF value required to maintain pregnancy.

CONCLUSIONS

PIBF serum value of pregnant women ≤ 20 weeks with threatened abortion were significantly lower

compared to normal pregnancy. This also showed that PIBF value could be used as a biomarker of a pathologic process in pregnancy. PIBF could also be used as a rational therapy in threatened abortion. Further prospective studies are required to determine the cut-off point of PIBF value necessary to maintain pregnancy.

REFERENCES

1. Formosa M. The paradox of pregnancy: an update on the immunology of early pregnancy. *Malta Med J.* 2008; 20(2): 10-4.
2. Hudic I, Fatušić Z. Progesterone-induced blocking factor (PIBF) and Th1/Th2 cytokine in women with threatened spontaneous abortion. *J Perinatal Med.* 2009; 37(4): 338-42.
3. Szekeres-Bartho J, Polgar B, Kelemen K, Par G, Szereday L, editors. Progesterone-mediated immuno modulation and anti-abortion effects: the role of the progesterone induced blocking factor. Poster presentation. 10th World Congress on the Menopause; 2002.
4. Kutteh WH. Recurrent pregnancy loss. In: Carr BR, eds. *Textbook of reproductive medicine.* In: edition, editor. Stamford, Connecticut: Appleton & Lange; 2004.
5. Polgár B, Nagy E, Mikó É, Varga P, Szekeres-Barthó J. Urinary progesterone-induced blocking factor concentration is related to pregnancy outcome. *Biol Reprod.* 2004; 71(5): 1699-705.
6. Haas DM, Ramsey PS. Progesterone for preventing miscarriage. *Cochrane Database Syst Rev.* 2013; 10.
7. Kalinka J, Szekeres-Bartho J. The Impact of Dydrogesterone Supplementation on Hormonal Profile and Progesterone-induced Blocking Factor Concentrations in Women with Threatened Abortion. *Am J Reprod Immunol.* 2005; 53(4): 166-71.
8. JH C. Check JH. Debate: should progesterone supplements be used? In: Carp HJA, editor. *Recurrent Pregnancy Loss Causes, Controversies and Treatment. 2: CRC Press;* 2015: 123-30.
9. Bainbridge DR. Evolution of mammalian pregnancy in the presence of the maternal immune system. *Reviews Reprod.* 2000; 5(2): 67-74.
10. Van Nieuwenhoven ALV, Heineman MJ, Faas MM. The immunology of successful pregnancy. *Hum Reprod Update.* 2003; 9(4): 347-57.
11. Bainbridge DR. Evolution of mammalian pregnancy in the presence of the maternal immune system. *Reviews Reprod.* 2000; 5(2): 67-74.
12. Schjenken JE, Paul JW, Tolosa JM, Smith R, Clifton VL. Mechanisms of maternal immune tolerance during pregnancy: INTECH Open Access Publisher; 2012.
13. Blois SM, Joachim R, Kandil J, Margni R, Tometten M, Klapp BF, et al. Depletion of CD8⁺ cells abolishes the pregnancy protective effect of progesterone substitution with dydrogesterone in mice by altering the Th1/Th2 cytokine profile. *J Immunol.* 2004; 172(10): 5893-9.
14. Dosiou C, Giudice LC. Natural killer cells in pregnancy and recurrent pregnancy loss: endocrine and immunologic perspectives. *Endocrine reviews.* 2005; 26(1): 44-62.

15. Stjernholm YV. Progesterone in Human Pregnancy and Parturition: INTECH Open Access Publisher; 2012.
16. Abadi A, Baziad A, Hestiantoro A. The benefits of progesterone therapy in imminent abortion. *Med J Indones*. 2005; 14(4): 258-62.
17. Kozma N, Halasz M, Polgar B, Poehlmann TG, Markert UR, Palkovics T, et al. Progesterone-induced blocking factor activates STAT6 via binding to a novel IL-4 receptor. *J Immunol*. 2006; 176(2): 819-26.
18. Menzies FM, Henriquez FL. Immuno modulation by the female sex hormones. *Open Infect Dis J*. 2009; 3: 61-72.
19. Margni RA, Gentile MT, Miranda S. Asymmetric antibodies: the antigen protective arm in a Th2-regulated immune response. *Inmunol*. 2002; 21(1): 29-35.
20. Speroff L, Fritz MA. Recurrent early pregnancy loss. *Clin Gynecol Endocrinol Infertil*. 2005: 1069-101.
21. Griebel CP, Halvorsen J, Golemon TB, Day AA. Management of spontaneous abortion. *Am Fam Physician*. 2005; 72(7): 1243-50.
22. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. *Reviews in Obstet Gynecol*. 2009; 2(2): 76.
23. Salomon LJ, Rozenberg P, Szekeres-Bartho J, Malagrida L, Giudicelli Y, Ville Y. Changes in progesterone-induced-blocking-factor expression rates following mifepristone administration in termination of pregnancy at 5 to 8 weeks. *J Maternal-Fetal Neonatal Med*. 2005; 17(5): 353-6.
24. Mesiano S. The endocrinology of human pregnancy and fetoplacental neuroendocrine development. *Yen and Jaffe's reproductive endocrinology* 6th ed Philadelphia: Saunders Elsevier. 2009: 104.

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

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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 PPRM 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 PPRM 17.43 ng/ml $\pm$ 12.4 ng/ml and without PPRM 8.45 ng/ml $\pm$ 6.86 ng/ml. The mean serum levels of MMP-9 in patients with PPRM 8.77 ng/ml $\pm$ 4.41 ng/ml, and without PPRM 4.46 ng/ml $\pm$ 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 PPRM and without PPRM.

[Indones J Obstet Gynecol 2017; 5-4: 199-202]

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 $\pm$ 12,4 ng/ml dan tanpa ketuban pecah dini 8,45 ng/ml $\pm$ 6,86 ng/ml. Rerata kadar serum MMP-9 pada pasien ketuban pecah dini kehamilan preterm 8,77 ng/ml $\pm$ 4,41 ng/ml, dan tanpa ketuban pecah dini 4,46 ng/ml $\pm$ 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.

[Maj Obstet Ginekol Indones 2017; 5-4: 199-202]

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

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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 placentar, 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 PPRM is 8-10% in pregnant women, and according to the Journal of Health Sciences Management and Public Health in 2006, the incidence of the PPRM 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 PPRM 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 PPRM. 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 extra-cellular.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 PPRM 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 PPRM 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 $\pm$ SD	p value
Preterm Premature Rupture of Membranes	24	17.43 $\pm$ 12.40	0.004
without Premature Rupture of Membranes	24	8.45 $\pm$ 6.86	

Table 1 shows the mean serum levels of TNF- α in patients with PPRM 17.43 ng/ml $\pm$ 12.4 ng/ml and without PPRM 8.45 ng/ml $\pm$ 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 $\pm$ SD	p value
Preterm Premature Rupture of Membranes	24	8.77 $\pm$ 4.41	0.000
without Premature Rupture of Membranes	24	4.46 $\pm$ 3.04	

Table 2 shows the mean serum levels of MMP-9 in patients with PPROM 8.77 ng/ml $\pm$ 4.41 ng/ml, and without PROM 4.46 ng/ml $\pm$ 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 PGF2 α 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 11 β -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 releasing 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 PPRM and preterm delivery spontaneous.¹²

In the case of PPRM, 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-1 β in the amniotic fluid found increased.¹

CONCLUSIONS

The mean serum levels of TNF- α in patients with PPRM 17.43 ng/ml $\pm$ 12.4 ng/ml and without PPRM 8.45 ng/ml $\pm$ 6.86 ng/ml. The mean serum levels of MMP-9 in patients with PPRM 8.77 ng/ml $\pm$ 4.41 ng/ml, and without PPRM 4.46 ng/ml $\pm$ 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 PPRM and without PPRM.

REFERENCES

1. Anna L Mariana. Premature rupture of membrane. England: Obstetric Evidence Based Guidelines: 2007: 138-48.
2. Goldenberg RL, Culhane JF, Romero R. Epidemiology and causes of preterm birth. *Lancet*, 2008; 371: 75-84.
3. Mohammad Sabri A Razzak, Mohammad A K Al-Sa'adi. The Role of Tumor Necrosis Factor-Alpha (TNF- α) in The Induction of Preterm Labor. *Karbala J. Med.* 2010; 31-2.
4. Kementerian Kesehatan. Survei Dasar Kesehatan Indonesia. Jakarta: Kemenkes: 2012.
5. Cunningham. Ketuban Pecah Dini, Williams Obstetrics ed 24. United States: Mcgraw-Hill Education: 2014; 180-98.
6. Riyani. Extreme preterm premature rupture of membranes: Risk factors and fetomaternal outcomes. *Oman Med J*, 2013; 28(2): 108-11.
7. Ping Xu. Expression of matrix metalloproteinase (MMP) - 2 and MMP-9 in human placenta and fetal membranes in relation to preterm and term labor. *Am J Embriol Metabol.* 2002; 25(3): 5-15.
8. Samuel P Jerome. Mechanism of premature rupture of membranes *New Eng J Med*, 2006; 12(4): 3-12.
9. Santolaya J. Prelabour rupture of membranes, Third edition *Clinical Obstetric. America: Blackwell published: 2013; 23(1): 2-9.*
10. Yonemoto Kanasi. Changes in Matrix Metalloproteinase (MMP)-2 and MMP-9 in fetal Amnion and Chorion During Gestation. Japan: Department of obstetrics and gynecology Juntendo university school of medicine: 2006; 132-48.
11. Hatice Robert M. Prolidase, Matrix Metalloproteinases I and I 3 Activity, Oxidate-Antioxidative Status as a Marker of Pre-term Premature Rupture of Membranes and Chorioamnionitis in Maternal vaginal Washing Fluids. *Int J Med Scien Turk: 2013. 13(4): 2-8.*
12. Rangaswamy Gifari. Weakening and Rupture of Human Fetal Membran-Biochemistry and Biomechanics Department of Pathology, case western reserve university, Cleveland, Ohio, USA: 2014, 231-45.

Research Article

The Role of Matrix Metalloproteinase-9 (MMP-9) in Endometriosis

Peran Matriks Metalloproteinase-9 (MMP-9) pada Endometriosis

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Abstract

Objective: To investigate the role of MMP-9 expression in endometriosis.

Methods: The study was conducted from October 2015 to March 2016, an observational study with cross-sectional design. Samples are all endometriosis patients who underwent laparoscopic surgery in Dr. Wahidin Sudirohusodo Hospital and several other hospitals in Makassar. Samples were stored and fixed in the Grand Medika Histopathology Laboratory Makassar for examination the expression of MMP-9 using immunohistochemical methods. Conducted an analysis of 50 samples, of which 11 samples of stage II, 21 stage III samples, and 18 samples of stage IV. The data obtained and analyzed statistically using Mann Whitney and Chi Square test with a significance level of $p < 0.05$.

Results: The results reported rankings mean the expression of MMP-9 in stage I-II = 16.68, stage III-IV 27.99 ($p = 0.013$). There were differences in the expression of MMP-9 based on the stage. Stage I-II endometriosis had a more positive 2 expression of MMP-9 (45.5%), stage III-IV endometriosis have more positive 3 expression of MMP-9 (59.0%). The results of chi square test ($p = 0.043$).

Conclusion: Higher expression of MMP-9 is significantly associated with higher degree of endometriosis.

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Keywords: matrix metalloproteinase-9, stages of endometriosis

Abstrak

Tujuan: Mengetahui peran matriks metalloproteinase-9 (MMP-9) dengan derajat berat ringannya endometriosis.

Metode: Penelitian dilakukan dari bulan Oktober 2015 sampai Maret 2016, merupakan penelitian observasional dengan desain potong lintang (cross sectional study). Sampel adalah semua penderita endometriosis yang menjalani operasi laparoskopi di RS Dr. Wahidin Sudirohusodo dan beberapa rumah sakit lain di Makassar. Sampel disimpan dan difiksasi pada Laboratorium Histopatologi Grand Medika Makassar untuk pemeriksaan ekspresi MMP-9 jaringan dengan menggunakan metode imunohistokimia. Dilakukan analisis terhadap 50 sampel, di mana 11 sampel stadium II, 21 sampel stadium III, dan 18 sampel stadium IV. Data yang diperoleh kemudian dianalisa statistik menggunakan uji Mann Whitney dan uji Chi Square dengan tingkat kemaknaan $p < 0,05$.

Hasil: Penelitian menunjukkan Rerata rangking ekspresi MMP-9 pada stadium I-II = 16,68, stadium III-IV 27,99 ($p = 0,013$). Stadium endometriosis I-II lebih banyak mempunyai ekspresi MMP-9 positif 2 (45,5%), stadium endometriosis III-IV lebih banyak mempunyai ekspresi MMP-9 positif 3 (59,0%).

Kesimpulan: Ekspresi MMP-9 berkaitan dengan derajat keparahan endometriosis.

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Kata kunci: matriks metalloproteinase-9, stadium endometriosis

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INTRODUCTION

Endometriosis is a chronic gynecological disorder that is dependent on estrogen levels (estrogen-dependent). It is usually associated with pelvic pain and infertility. It is characterized by the presence of endometrial tissue on the outside of the uterus, most commonly in the pelvic, peritoneum or ovaries, but can also occur in recto-vaginal septum and rare in pleural, pericardial or brain. Its prevalence is estimated to be 6-10% in general woman population and 35-50% of patients experience pain and or infertility. The actual prevalence and incidence of endometriosis in the

general population is not clear. Preciado et al investigated the infertile woman with endometriosis at age 30.3 ± 3.9 years, while the incidence of endometriosis in 197 infertile women was 68 people (34.5%).¹

At the clinical level, endometriosis has a significant impact on a variety of subjective and objective changes, especially in terms of pain (dysmenorrhea, dyspareunia, diskezia), infertility and menstruation impaired. Social impact of this disease is the other side need to be considered by practitioners. Since the etiology and pathogenesis of endometriosis is still an enigma, the treatment is still a controversy.

Endometriosis is accompanied by increased secretion of pro-inflammatory cytokines, impaired cell-mediated immunity, neo-angiogenesis and endometrial reflux anomalies. To date, many of analysis of cytokines have been done thought to be involved in endometriosis. Many factors contribute to triggering, one of them is a metalloproteinase matrix (MMP), a family of zinc-dependent endopeptidase that regulate the integrity and composition of the extracellular matrix. MMP plays an important role in cell proliferation, migration, differentiation, angiogenesis, apoptosis, and immune system. Dysregulation of MMP has implications in various diseases including tumor growth. The initial phase of endometriosis is the degradation and remodeling of the extracellular matrix and increased expression of MMP.²

Among the various MMP, found over-expression of metalloproteinase-9 matrix (MMP-9) in different types of tumor. In mouse model, found the role of MMP-9 in terms of the process of invasion, aggression, and tumor metastases.³ High expression of MMP-9 is an indicator of the progression of tumor growth, reduced survival rate, and increased metastases.

The previous studies evaluating the role of MMP in endometriosis had been done with different techniques and materials. Increased expression of MMP-9 was higher in ectopic endometrium (endometriosis) than eutopic endometrium and higher in severe endometriosis.^{4,5} However, the study of the role of MMP-9 as endometriosis marker still less common in Indonesia, especially in South Sulawesi.

This study aimed to evaluate the correlation between the expression of Metalloproteinase Matrix-9 (MMP-9) and the severity of endometriosis.

METHODS

This was a cross-sectional study. This study was conducted at several teaching hospitals in Makassar, South Sulawesi, including Dr. Wahidin Sudirohusodo Hospital and other private hospitals used as the teaching hospital networking. The tissue samples of endometriosis cyst that had been fixed were kept at Histopathology Laboratory Grand Medika Makassar for examination the expression of MMP-9. This study was conducted from October 2015 to March 2016. Samples were

all patients with endometriosis who underwent laparoscopic surgery. Data were analyzed using Mann Whitney and Chi Square test. P values less than 0.05 were considered as statistically significant.

RESULTS

Table 1 shows the characteristics of the patients. Majority of the patients were in stage III-IV of endometriosis (78%), while stage I-II of 22%. The percentage of women who experienced dysmenorrhea were 54%, a history of infertility (56%), the age of older 35 years old (56%), married (92%), normal weight (56%) and did not use contraception (82%).

Table 1. The Characteristics of the Patients.

Characteristics	Amount (n)	Percentage (%)
Stage of Endometriosis		
I - II	11	22
III - IV	39	78
Dysmenorrhea		
Yes	27	54
No	23	46
Infertile		
Yes	28	56
No	22	44
Age Group		
≤ 35	22	44
> 35	28	56
Marital Status		
Yes	46	92
No	4	8
BMI		
Normoweight	28	56
Overweight	22	44
Contraception		
Yes	9	18
No	41	82

Table 2 shows the stages of endometriosis based on the characteristics of the patients. Most of the patients stage I-II endometriosis may experience more dysmenorrhea (63.6%), infertility (72.7%), the age of less than or equal to 35 years old

(54.5%), married (90.9%), normal weight (72.7%) and did not use contraception (100%). Patients stage III-IV endometriosis may experience more dysmenorrhea (51.3%), infertility (51.3%), the age of older 35 years old (59.0%), married (92.3%), normal weight (51.3%) and did not use contraception (76.9%).

Table 2. Stages of Endometriosis Based on the Characteristics of the Patient.

Characteristics	I-II		III-IV		Amount	
	n	%	n	%		
Dysmenorrhea						
Yes	7	63.6	20	51.3	27	54
No	4	36.4	19	48.7	23	46
Infertile						
Yes	8	72.7	20	51.3	28	56
No	3	27.3	19	48.7	22	44
Age Group						
≤ 35	6	54.5	16	41.0	22	44
> 35	5	45.5	23	59.0	28	56
Marital Status						
Yes	10	90.9	36	92.3	46	92
No	1	9.1	3	7.7	4	8
BMI						
Normoweight	8	72.7	20	51.3	28	56
Overweight	3	27.3	19	48.7	22	44
Contraception						
Yes	-	-	9	23.1	9	18
No	11	100.0	30	76.9	41	82

Table 3 shows the differences between the average ranking of expression of MMP-9 based on the stage of endometriosis. The average ranking of the expression of MMP-9 in stage I-II was 11.36, stage III-IV of 29.49. Statistical test results obtained by Mann Whitney, p value = 0.000. It is suggested that there are differences in the expression of MMP-9 based on the stage, where the higher stages of endometriosis, then the higher the expression of MMP-9.

Table 3. The Differences between the Average Ranking of Expression of MMP-9 Based on the Stage of Endometriosis

Stage of Endometriosis	The Average Ranking Of MMP-9	Significance (p)
Stage I-II	16.68	0.013
Stage III-IV	27.99	

Table 4 shows the association between the stage of endometriosis and the expression of MMP-9. The Patients who had stage I-II endometriosis have more expression of MMP-9 positive 2 (45.5%), stage III-IV endometriosis have more expression of MMP-9 positive 3 (59.0%). The result of Chi Square test was obtained value p = 0.043. This suggested that there is an association between the stage of endometriosis and the expression of MMP-9.

Table 4. The Association between the Stage of Endometriosis and the Expression of MMP-9.

MMP-9 Expression	Stage of Endometriosis						Significant (p)
	I-II		III-IV		Total		
	n	%	n	%	n	%	
Positive 1	4	36.4	5	12.8	9	18.0	0.043
Positive 2	5	45.5	11	28.2	16	32.0	
Positive 3	2	18.2	23	59.0	25	50.0	
Total	11	100.0	39	100.0	50	100.0	

DISCUSSION

The study showed an increased expression of MMP-9 in the tissue and parallel with increasing the stage of endometriosis. More than 10% of women have endometriosis. Most of them have no or only little complains of symptoms, thus the prevalence of severe endometriosis (stage III-IV) more than mild endometriosis (stage I-II). Some women complain of severe dysmenorrhea, chronic pelvic pain, and dyspareunia. Symptoms depend on the location, distribution, and depth of endometrium implantation, the presence and severity of adhesions, the presence and size of ovarian endometrioma. A study by Ragab et al involving 654 young adult women with endometriosis found that 48.9% of the subjects complained menstrual pain, and 68.8% reporter severe dysmenorrhoea.⁶ A retrospective study by Andres et al involving 394 patients showed that dysmenorrhoea affects 80.9% young adult patients (severe dysmenorrhoea of 33.3%) and chronic pelvic pain of 66.6%.⁷

The mean age of patients with endometriosis varies 31.1 ± 10.4 years (between 17-53 years old), mostly 30-35 years.⁸ According to the theory, the true prevalence of endometriosis is unknown, but approximately 5-10% of women in reproductive age (menarche to menopause). The peak age is 25-

30 years old, and is rare in young women or postmenopausal women.

Macer et al revealed that women with mild endometriosis showed a decrease in the pregnancy rate after 3 years compared to women with unexplained infertility (36 vs 55%).⁹ Brosens et al conducted a study of IVF, and they concluded that in women with severe endometriosis, decreased ovarian reserve, decreased embryo quality and total of oocytes, and decreased the implantation ratio. The correlation between endometriosis and infertility is supported by the literature.¹⁰

The study by Yi et al, including 481 women with endometriosis, stage I by 153 women, stage II by 113, stage III by 110, and stage IV by 105, showed that women with severe stage (III-IV) were associated with low BMI, compared to patients with minimal or mild stage (I-II), and BMI was significantly related to the stage of disease.¹¹

In this study, there was significant association between the expression of MMP-9 based on the stage of endometriosis, where the higher stages of the disease, the higher the expression of MMP-9. The immunohistochemical study of 20 cases with endometriosis showed that MMP-1, -2, and -9 were strongly detected in the stroma and epithelial cells.¹² This study supported by Chen et al, showed that increased MMP-9 occurred in ectopic endometrium. Collette et al. revealed that increased proteolytic activity of eutopic endometrium occurred in women with endometriosis than normal women, where found an increase in MMP-9 and a decrease in its natural inhibitor.¹³

The pathogenesis of endometriosis regarding attachment-aggression-angiogenesis (AAA) scheme has been generally accepted. In this process, the role of MMP was uncontested. MMP is a family of zinc-dependent endopeptidase that can degrade extracellular collagen and matrix components. The formation of ectopic endometrial tissue mediated by factors that facilitate adhesion to peritoneal cavity include cell growth, increased aromatase activity, angiogenic, neuralgenic/lymphogenic factors, and reinforced by the activity of MMP. MMP regulated migration, infiltration, proliferation and apoptosis of cells. MMP-2 and MMP-9 are two members of the MMP family that is the most powerful in degrading collagen IV. In order to occurred adhesion and infiltration, structural changing should be occurred in the tissue by the extracellular membrane degradation

and MMP play a role in accelerating neovascularization.^{13,14}

Swarnakar et al stated that the synthesis of MMP-9 was correlated positively to the stage of the disease, where a correlation between focal inflammatory pelvic endometriosis was found, as consequence found improved functioning of immune cells in the peritoneal cavity.¹⁵ MMP-9 is mainly synthesized and secreted by macrophages and neutrophils.¹⁶ In peritoneal fluid, found a large number of derivate-macrophages substance, resulting in increased levels of MMP-9 in the peritoneal fluid of patients with endometriosis, in line with the severity of the stadium. Once ectopic endometrium was implanted in the peritoneum, a large number of MMP was expressed by autocrine and paracrine cytokine activation, thereby increasing the extracellular matrix degradation that contribute to further growth of the endometrium. This is also consistent with a recent study by Liu et al, involving 100 patients with endometriosis, including ectopic endometrium and eutopic endometrium, and patients with uterine myoma as controls. Blood and acites fluid sampling were performed to evaluate the level of MMP-9 using zimogram and enzyme-linked immunosorbent assay (ELISA). The results showed a significant correlation between MMP-9 and the location of the endometrium, clinical stage, and the proliferation cycle ($p < 0.005$).⁴

The different result reported by Gilabert-Estelles et al, that get the insignificant expression of MMP-9 in the immunohistochemical examination of endometrial and ovarian tissue of endometriosis patients, the study revealed a new theory that the activity of proteolytic enzymes such as protease and gelatinase (MMP 2 and MMP-9) is likely to be only increased in the early formation of endometriosis implants, but when cysts/endometrioma formed, proteolytic activity was not found anymore, only the levels of inhibitors such as PAI-1 and TIMP-1 is relatively increased, although not in all cases. These findings may elucidate the operative clinical implications where endometrioma cysts are often found in the absence of adhesions and expansion into the surrounding tissue of the ovary.¹⁷

CONCLUSIONS

We found that higher MMP-9 expression is associated with higher degree of endometriosis.

REFERENCES

- Preciado R, Torres CJ, Zuniga-Montiel JA, Martinez CJ, Manterola AD, Garcia LA. Incidence of endometriosis in infertile women: clinical and laparoscopic characteristics. *Ginecol Obstet Mex.* 2015; 73(9): 471-6.
- Angulo JC, Ferruelo A, Rodriguez-Barbero JM, Nunez C, de Fata FR, Gonzales J. Detection and molecular staging of bladder cancer using real-time RT-PCR for gelatinases (MMP-2, MMP-9) and TIMP-2 in peripheral blood. *Actas Urol Esp.* 2011; 35(3): 127-36.
- Bruner KL, Matrisian ML, Rodgers WH, Gorstein F, Osteen KG. Suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice. *J Clin Invest.* 1997; 99(12): 2851-7.
- Liu XJ, He YL, Peng DX. Expression of metalloproteinase-9 in ectopic endometrium in women with endometriosis. *Di Yi Jun Yi Da Xue Xue Bao.* 2002; 22(5): 467-9.
- Ueda M, Yamashita Y, Takehara M, Terai Y, Kumagai K, Ueki K, et al. Survivin gene expression in endometriosis. *J Clin Endocrinol Metabol.* 2000; 87(7): 3452-9.
- Ragab A, Shams M, Badawy A, Alsammani MA. Prevalence of Endometriosis Among Adolescent School Girls with Severe Dysmenorrhea: A Cross Sectional Prospective Study. *Int J Health Sci (Qassim).* 2015; 9(3): 273-81.
- Andres MP, Podgaec S, Carreiro KB, Baracat EC. Endometriosis Is An Important Cause Of Pelvic Pain In Adolescence. *Rev Assoc Med Bras.* 2014; 60(6): 560-4.
- Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of Endometriosis on Women's Lives: A Qualitative Study. *BMC Women's Health.* 2014; 14: 123.
- Macer ML, Taylor HS. Endometriosis and Infertility A Review of the Pathogenesis and Treatment of Endometriosis-associated Infertility. *Obstet Gynecol Clin North Am.* 2012; 39(4): 535-49.
- Brosens I. Endometriosis and the Outcome of In Vitro Fertilization. *Fertil Steril.* 2004; 81(5): 1198-200.
- Yi K, Shin JH, Park MS, Kim T, Kim SH, Hur YJ. Association of body mass index with severity of endometriosis in Korean women. *Int J Gynecol Obstet.* 2009; 105(1): 39-42.
- Mizumoto H, Saito T, Ashihara K, Nishimura M, Takehara M, Tanaka R. Expression of matrix metalloproteinases in ovarian endometriomas: immunohistochemical study and enzyme immunoassay. *Life Sci.* 2002; 71(3): 259-73.
- Chen Q, Qiu N, Pu D, Zhou Y, Li T, Yang H. Change Profiles in Matrix Metalloproteinase-2 and -9 in Induced Endometriosis in Mice. *J Huazhong Univ Sci Technol Med Sci.* 2010; 30(2): 188-92.
- Malvezzi H, Aguiar VG, Paz CC, Tanus-Santos JE, Penna IA, Navarro PA. Increased Circulating MMP-2 Levels in Infertile Patients with Moderate and Severe Pelvic Endometriosis. *Reprod Sci.* 2013; 20(5): 557-62.
- Swarnakar S, Paul S. Curcumin arrests endometriosis by down regulation of matrix metalloproteinase-9 activity. *Indian J Biochem Biophys.* 2009; 46(1): 59-65.
- Long L, Cao Y, Tang LD. Transmembrane estrogen receptor GPR30 is more frequently expressed in malignant than benign ovarian endometriotic cysts and correlates with MMP-9 expression. *Int J Gynecol Cancer.* 2012; 22(4): 539-45.
- Gilbert-estelles J, Estelles A, Gilbert J, Castello R, Espana F, Falco C et al. Expression of several components of the plasminogen activator and matrix metalloproteinase systems in endometriosis. *Hum Reprod.* 2003; 18(7): 1516-22.

Research Article

The Menopausal Symptoms of Paramedics at a Tertiary Care Center

Gejala Menopause Paramedis pada suatu Layanan Kesehatan Tersier

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Abstract

Objective: To assess paramedic menopausal symptoms on the inpatient unit and outpatient unit.

Methods: This was a cross sectional study. Data collect by fill the questioner, the questioner fill by menopausal paramedic on Prof. Dr. R. D. Kandou Manado Hospital from October 2016 to January 2017. Data were analyzed using SPSS 22.0 for Windows.

Results: Of 60 paramedics, 30 were divided to inpatient unit and the other 30 were divided to outpatient unit. By the menopause rating scale, somatic and urogenital complaint in statistical test have no significant differences. Psychology complaint with a moderate complaints on inpatient unit have 19 paramedic (63%) and 12 paramedic (40%) on outpatient paramedic, in statistical have a significant differences ($\chi^2=9.62$, $p=0.022$). On the total score menopausal complaints, the moderate complaints 18 paramedic (60%) on the inpatient unit and the minor complaints 21 paramedic (70%) on the outpatient unit, in statistical have a significant differences ($\chi^2=6.97$, $p=0.031$).

Conclusion: There is no significant difference in somatic and urogenital complaints on paramedic inpatient unit and outpatient unit. There is a significant difference in psychological complaints and total score menopausal complaints on paramedic inpatient unit and outpatient unit.

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Keywords: menopause, menopause rating scale, paramedic

Abstrak

Tujuan: Membandingkan keluhan menopause pada paramedik instalasi rawat inap dan rawat jalan.

Metode: Penelitian ini adalah deskriptif analitik dengan rancangan potong lintang. Pengumpulan data berupa pengisian kuesioner, kuesioner diisi oleh paramedik instalasi rawat inap dan rawat jalan masa menopause di RSUP Prof. Dr. R.D. Kandou Manado yang memenuhi kriteria inklusi dan eksklusi, penelitian ini dilakukan sejak bulan Oktober 2016 sampai bulan Januari 2017. Data dianalisis dengan SPSS versi 22.0.

Hasil: Dari 60 orang paramedis yang memenuhi kriteria inklusi, terbagi menjadi 30 paramedis instalasi rawat inap dan 30 paramedis instalasi rawat jalan. Berdasarkan skala menopause skala rating, keluhan somatik dan keluhan urogenital dari uji statistik tidak terdapat perbedaan yang bermakna. Keluhan psikologis dengan keluhan sedang pada paramedik instalasi rawat inap 19 orang (63%) dan 12 orang (40%) pada paramedik instalasi rawat jalan, secara statistik terdapat perbedaan yang bermakna ($\chi^2=9.62$, $p=0.022$). Pada total skor keluhan menopause didapatkan keluhan sedang 18 orang (60%) pada paramedik instalasi rawat inap dan keluhan ringan 21 orang (70%) pada paramedik instalasi rawat jalan, secara statistik terdapat perbedaan yang bermakna ($\chi^2=6.97$, $p=0.031$).

Kesimpulan: Tidak terdapat perbedaan bermakna pada keluhan somatik dan urogenital paramedik instalasi rawat inap dan rawat jalan masa menopause. Terdapat perbedaan yang bermakna pada keluhan psikologis dan skor total keluhan menopause paramedik instalasi rawat inap dan instalasi rawat jalan masa menopause.

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Kata kunci: menopause, menopause rating scale (MRS), paramedik

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INTRODUCTION

Menopause, a permanent cessation of the menstrual cycle, is feared by majority of the women worldwide. Several symptoms of menopause can affect daily activities. Unfortunately, most women are not aware of the changes that are caused by menopause. These symptoms occurred due to decreased estrogen levels in women during peri-menopause, menopause, and post menopause.¹

Each year, approximately 25 million women around the world would enter menopausal phase. Women aged over 50 years around the world increased from 500 million to over one billion in 2030. According to the World Health Organization (WHO), in 2025 the number of older women will increase from 107 million to 373 million in Asian countries.² In Indonesia, based on the population census in 2000, the number of women over 50 years old who have entered menopause as many

as 15.5 million people, and in 2020 an estimated 30.3 million person.³ Data derived from Yasmin Clinic in 2010-2012 suggested that the average age of menopause was 51.38.⁴ Deddy et al, in a study on the quality of life menopausal women with menqol scale on Manado in 2015 mention that the average age of menopause in Manado was 50.81 and that most complaints were physical complaints (93% of 563 subjects).⁵

There are various scales to measure level of the menopause complaints, but menopause rating scale (MRS) is the most efficient scale compared to the other scales because the scale only 11 assessment. Menopause rating scale (MRS) was developed in the early 90s to measure level of the complaints, and was associated with menopause age, by assessing a number of specific symptoms. To determine the scale of the complaints or symptoms, statistical methods are used to identify the three dimensional complaints: complaints somatic, psychological, and urogenital.⁶

Female paramedics are not spared from the menopause. Paramedics as a workers in the hospitals, paramedics are in charge of health services in the form of nursing care such as bio-socio-cultural and spiritual to the patient, family, and community either healthy or sick. Too much complaints and requests from the patients would increase paramedics workload and stress levels. Not only from the patient who makes paramedics exhaustion of the physical, emotional and mental but from patient's family and colleagues who can not cooperate.⁷ Several studies suggested that menopausal complaints with a high workload have a many complaints compared a low workload.⁸ This study is aimed to investigate the difference between the complaints and severity of complaints among paramedics inpatient unit and outpatient unit on menopause phase.

METHODS

This was across sectional study. Data were collected by having the paramedics filling the questionnaire, the questioner fill by menopausal phase paramedics inpatient unit and outpatient unit in the Prof. Dr. R. D. Kandou Manado hospital.

This study was conducted at Prof. Dr. R.D. Kandou Manado hospital, from October 2016 to January 2017. The sample required was 60 paramedics menopause divided into 30

paramedics inpatient and 30 paramedics outpatient. The sample is all the menopause female paramedic in the inpatient unit and outpatient unit of the Prof. Dr. R.D. Kandou Manado hospital during the research period and meet the inclusion and exclusion criteria.

This study assessed with Menopause Rating Scale (MRS). Menopause Rating Scale (MRS) consists of 11 items that assess symptoms of menopause which is divided into three sub-scales: somatic - hot flushes, heart discomfort, sleep disorders and muscle and joint problems (items 1-3 and 11), psychological - depressive mood, irritability, anxiety and mental and physical fatigue (items 4-7), and urogenital problems - sexual, bladder problems and vaginal dryness (8-10 items). Each item can be judged by the subject from 0 (none) to 4 (1 = mild, 2 = moderate, 3 = severe, 4 = very severe). Per each subscale total score is the sum of each item assessed contained in subscale. MRS total score is the sum of the scores obtained for each subscale. If found severe menopausal complaints on paramedics it will be counseling for menopause clinic in the Prof. Dr. R. D. Kandou Manado hospital.

Data collection by the researcher. All statistical analyses were performed using SPSS version 22.0.

RESULTS

This study was conducted during the period of October 2016 to January 2017 at the Prof. Dr. R. D. Kandou Manado hospital on menopausal paramedics inpatient unit and outpatient unit, with a total sample of 60 menopausal paramedics, divided into 30 menopausal paramedics inpatient unit and 30 outpatient menopausal paramedics out patient unit.

Table 1. Characteristics of the Subjects

Variable	Inpatient Unit		Outpatient Unit	
	n	%	n	%
Age (Years)				
45-50	5	17	3	10
51-55	25	83	27	90
Marital Status				
Married	26	86	25	83
Not Married	2	7	2	7
Widow	2	7	3	10

Education				
SPK	7	23	5	17
Diploma	12	40	19	63
S-1	11	37	6	20
Parity				
Nullipara	3	10	5	17
Primipara	10	33	12	40
Multipara	17	57	13	43
Grande Multipara	0	0	0	0
BMI				
Normoweight	20	67	16	53
Overweight	8	26	11	37
Obese	2	7	3	10

DISCUSSION

Table 1 explained about the characteristic of paramedics at menopause in-patient clinic and out-patient clinic. There are about 17% of paramedic at menopause in-patient clinic, and about 10% at out-patient clinic, based on age group of 45-50 years old. The most get in are paramedics on the age group of 51-55 years old, who are about 83% at in-patient clinic and 90% at out-patient clinic.

The menopausal age of paramedics in this study are suitable with some studies and datas. The datas were established in Klinik Yasmin on 2010-2012 with the average of menopause age is 51.38 years.⁴ In Suryanto et al study about the quality of life in menopause women at menopause out-patient clinic RSUP Prof. Dr. R. D. Kandou Manado with cross sectional study on 2011 mentioned that the average age of menopausal women in Manado is 51 years old.⁹ A study by Deddy et al on 2015 found that the average age of menopause women in Manado is 50.81.⁵

The marital status of paramedics at in-patient clinic which also being the subject of this study, with most subjects status are marriage (86%), also the paramedics at out-patient clinic with the most status are marriage (83%). Based on the level of education we found that most of the paramedic at in-patient clinic are diploma (40%) and most in out-patient clinic are also diploma (63%). Gold E.D. et al study on 2001 found no significant association between education as well as marital status and menopause. Moreover, they found no effect of heavy work with early menopause.¹⁰

Based on number of children (parity), the most get in are paramedics with multi parity (57%) at menopause in-patient clinic, which also happened at out-patient clinic with the most get in are multi parity (43%). In some studies races, parity and body heights were not affecting the age of menopause. But, according to Herman et al on 2002 based on two cross sectional studies found that the longer of menopause age occurred because of the number of parity.¹¹

Based on BMI, most of the paramedics at in-patient and out-patient clinic were normo-weight. The BMI of in-patient clinic paramedics with 67% were normoweight and the BMI of out-patient clinic paramedics with 53% were normoweight. As observed with BMI, some studies revealed that women with malnutrition or thin tend to have

Table 2. Comparison Table the Severity of Complaints

Variable	Inpatient Unit		Outpatient Unit		p value
	n	%	n	%	
Somatic Complaints					
Asymptomatic (0-2)	6	20	11	37	X ² =5.79 p=0.055
Mild (3-4)	8	27	12	40	
Moderate (5-8)	16	53	7	23	
Severe (≥9)	0	0	0	0	
Psychological Complaints					
Asymptomatic (0-1)	4	13	9	30	X ² =9.62 p=0.022
Mild (2-3)	5	17	12	40	
Moderate (4-6)	19	63	8	27	
Severe (≥7)	2	7	1	3	
Urogenital Complaints					
Asymptomatic (0)	6	20	10	34	X ² =1.52 p=0.47
Mild (1)	18	60	16	53	
Moderate (2-3)	6	20	4	13	
Severe (≥4)	0	0	0	0	

Table 3. Total Score Table of Complaints

Menopause Complaints	Inpatient Unit		Outpatient Unit		p value
	n	%	n	%	
Asymptomatic (0-4)	1	3	1	3	$X^2=6.97$ p=0.031
Mild (5-8)	11	37	21	70	
Moderate (9-16)	18	60	8	27	
Severe (≥ 17)	0	0	0	0	

early menopause. This happened as the result of body fat which produce estrogen, so malnourished women or thin women with less body fat will tend to have early menopause.¹¹

Table 2 explains about the comparison of symptoms severity at menopause in-patient and out-patient clinic paramedics. These symptoms severity divided into three complaints: somatic complaints, psychological complaints, and urogenital complaints.

The comparison of somatic complaints at in-patient clinic paramedics with the most complaints are moderate complaints (53%), while paramedics at out-patient clinic also having moderate complaints (23%). Paramedics at menopause out-patient clinic with the most complaints are mild complaints (40%), while at menopause in-patient clinic are mild complaints (27%). According to statistic test with Chi-square found the value $p > 0.05$ ($p = 0.055$), this showed that there is no significant correlation in somatic complaints between paramedics at both menopause in-patient and out-patient clinic. The result of statistic test in this study is convenient with the study of Chuni et al on 2011, which they found that work load was not affect the somatic complaints in menopause, because in menopause, somatic complaints is caused by hormonal changing which is caused by the reduction of estrogen level which followed by the escalation of FSH and LH level. The symptoms usually happened between 1 to 2 years after menopause at most women, but can continue until 10 years or more at some women.¹²

The comparison of psychological complaints in paramedics at menopause in-patient clinic with the most complaints are moderate (63%), and paramedics at menopause out-patient clinic also with moderate complaints (27%). Paramedics at out-patient clinics with the most complaints are mild (40%), and paramedics at in-patient clinic with mild complaints are 17%. Based on statistic test with Chi-square found that $p < 0.05$ ($p = 0.022$), this showed that there is significant correlation of psychological complaints between paramedics at menopause in-patient and out-patient clinic. This study is not corresponding with the study from Siregar MFG et al. In Siregar MFG et al study on 2010 showed that statistically, there is no significant correlation in psychological complaints between paramedics in menopause age. This condition perhaps is caused by the educational

background in some correspondents and also the work scope in health department which caused them to understand the process of menopause, so they can accept the condition that can affect the psychological aspect cause by menopause age itself.⁸ While according to Chuni et al on 2011, there are statistically significance different in psychological aspects. Psychological complaints that emerge in menopause age not fully caused by the changing of hormonal, but related to physical problems, work load, and the health of menopause women.¹²

The comparison of urogenital complaints in paramedics at menopause in-patient clinic with the most complaints are mild complaints (60%), also at out-patient clinic with most are mild complaints (53%). Based on statistic test with Chi-square found that $p > 0.05$ ($p = 0.47$) this showed that there is no significant correlation between urogenital complaints in paramedics at menopause in-patient and out-patient clinic. This study is corresponding with the study by Safitri A on 2009. In Safitri A study explained that there is no correlation between activity and urogenital complaints in menopause women.¹³ While according to Chuni et al, conclude that statistically, urogenital complaints is higher in post menopause group than pre menopause group. There is no statistic differences in menopause women with different work activity. Very low estrogen production in menopause age will lead to atrophy of vaginal mucous surfaces, which is also accompanied by vaginitis, pruritus, dyspareuni, and stenosis. Loss of estrogen will cause the loss of collagen in vagina, adipose tissue, and the ability of holding water. As the vagina wall subside, the rugae will become smooth and vanished. The epithelium in the surface will loss the fibrous outside layer and then diminish into some cell layers and also the ratio of basal cell and superficial cell will reduce. The effect will cause vaginal surface being susceptible to bleed with minimal trauma. Genitourinary atrophy will lead to many symptoms that affect life quality, and causing dyspareuni which also leading to loss of sexual desire.

Table 3 explained about the comparison of total scoring of menopause complaints in paramedics at menopause in-patient and out-patient clinic. It have been found that most complaints in paramedics at in-patient clinic are moderate complaints (60%) while at out-patient clinic most complaints are mild complaints (70%). Based on statistic test

with Chi-square found that $p < 0.05$ ($p = 0.031$) this showed that there is significant correlation between complaints total score in paramedics at menopause in-patient and out-patient clinic. According to Safitri A, the regular physical activity and social activity will reduce the menopause complaints.¹³ Also the study from Febriansyah et al on 2015 said that good physical activity and good life quality will affect the menopause complaints.⁵ In this study, heavy work load and higher mental pressure are found in paramedics at menopause in-patient clinic than out-patient clinic. Because of that in this study, we found that paramedics at menopause in-patient clinic are having more menopausal complaints than at out-patient clinic. Chuni et al concluded the same thing where women complaints were based on total score that were measured by Menopause Rating Scale which is in heavier work load group will lead to elevate the menopause complaints.¹²

CONCLUSION

There is no significant correlation in somatic complaints between paramedics at menopause in-patient clinic and out-patient clinic. Also, there is no correlation between urogenital complaints in paramedics at menopause in-patient clinic and out-patient clinic. There is significant correlation in psychological complaints between paramedics at menopause in-patient clinic and out-patient clinic. Also, there is correlation in total score complaints between paramedics at menopause in-patient clinic and out-patient clinic.

SUGGESTION

Paramedics should have the education of menopause, so they can avoid stress and heavy physical activity and help to reduce complaints in menopause especially the psychological complaints, so that paramedics can enhance their qualities of life in menopause age. There should be more study to compare the amount of work hours and level of work activity in paramedic at menopause age, so that we can reduce the complaints they experience

in menopause age also will enhance their qualities of life and increase the performance of work between nurses, doctors and patients.

REFERENCES

1. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas*. 2009; 20, 62(2): 153-9.
2. World Health Organization. Women and Health: today's evidence tomorrow's agenda. World Health Organization; 2009.
3. Kowira M, Loho MFT, Wagey FW. Perbandingan kala MENQOL dengan Menopause Rating Scale (MRS) Pada Kualitas Hidup Wanita Menopause di Kota Manado. Tesis, Manado. PPDS-1 Obstetri dan Ginekologi FK UNSRAT; 2012.
4. Hestiantoro A, Natadisastra RM, Sumapraja K, Wiweko B, Pratama G, Situmorang H, et. al. Best Practice on IMPERIAL. Ed ke-1. Jakarta: Sagung Seto; 2012: 25.
5. Febriansyah D, Loho MFT, Sondakh J. Kualitas Hidup Perempuan Menopause Skala MENQOL Di Kota Manado. Tesis. Manado. PPDS-1 Obstetri dan Ginekologi FK UNSRAT; 2015.
6. Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle aged women with the Menopause Rating Scale. *Maturitas*. 2007; 20, 57(3): 271-8.
7. Lumintang P, Kumaat L, Mulyadi. Perbedaan Tingkat Stres Kerja Perawat Instalasi Gawat Darurat dan Unit Rawat Inap di Rumah Sakit Pancaran Kasih GMIM Manado. Manado. Program Studi Ilmu Keperawatan FK UNSRAT; 2015.
8. Silitonga HN, Siregar MFG, Hutapea H, Nasution S. Depresi dan Cemas Masa Perimenopause dan Pascamenopause pada Paramedis RSUP H Adam Malik dan RS Jejaring Medan. 2010.
9. Suryanto F, Loho MFT, Sondakh J. Kualitas Hidup Perempuan Menopause. Disampaikan pada PIT-POGI IX Jakarta. Juli 2011.
10. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol*. 2001; 1, 153(9): 865-74.
11. Schneider HP. The quality of life in the post-menopausal woman. *Best Practice & Research Clin Obstet Gynecol*. 2002; 16(3): 395-409.
12. Chuni N, Sreeramareddy CT. Frequency of symptoms, determinants of severe symptoms, validity of and cut-off score for Menopause Rating Scale (MRS) as a screening tool: a cross-sectional survey among midlife Nepalese women. *BMC women's health*. 2011; 11(1): 30.
13. Safitri A. Beberapa Faktor yang Mempengaruhi Menopause pada Perempuan di Kelurahan Titi Papan Kota Medan. Tesis. Medan. Universitas Sumatera Utara; 2009.

Research Article

Postplacental IUCD CuT380A: Acceptability, Effectivity and Side Effects

AKDR Cu T380A Pascaplasenta: Penerimaan, Efektivitas dan Efek Samping

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Abstract

Objective: To evaluate the acceptability, effectivity and side effects of Postplacental IUCD after vaginal delivery at Dr. Cipto Mangunkusumo Hospital (RSCM) after 6 month of insertion.

Methods: A prospective study was conducted at RSCM Jakarta during the period of August to October 2012. Postplacental IUCD was inserted into the subjects' uterus until it reached the fundus. Follow up was done at 40-42 days and 6 months after delivery.

Results: A total of 234 women were recruited in this study, with 19.2% loss of follow up. No significant difference on subjects' characteristics who came and loss of follow up in this study. Expulsion was experienced by 5.1% subjects (total expulsion 4.1% and partial 1%) at the first visit on 40-42 days and 7.5% subjects (total expulsion 0.6% and partial 6.9%) at the second visit, after 6 months. 9.3% subjects had the IUCD removed at the first and second visit. Among all of the subjects who had the IUCD removed by request or had the expulsion, 61% were willing to do reinsertion. The effectivity of IUCD was 100%, with 68.9% subjects was still breastfeeding. The side effects were vaginal discharge (23%), dysmenorrhea (4-21%), and spotting (2-10%).

Conclusion: The acceptability and effectivity of postplacental IUCD after 6 months were 86.8% and 100%. Cummulative expulsion rate were 12.6%, and the most common side effects were vaginal discharge, dysmenorea, and spotting.

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Keywords: acceptability, effectivity, expulsion rate, IUD, post-placenta

Abstrak

Tujuan: Mengevaluasi penerimaan, efektivitas dan efek samping AKDR pascaplasenta pada persalinan pervaginam di RSCM selama periode 6 bulan setelah pemakaian.

Metode: Penelitian observasional kohort prospektif dilakukan di RSCM Jakarta pada Agustus-Oktober 2012. Alat kontrasepsi dalam rahim (AKDR) pascaplasenta dipasang pada uterus hingga mencapai fundus uteri. Penilaian dilakukan pada kunjungan 40-42 hari pascasalin dan 6 bulan kemudian.

Hasil: Jumlah total subjek 234 orang, dengan 19,2% loss of follow up. Tidak terdapat perbedaan bermakna antara subjek yang datang dan loss of follow up. Ekspulsi terjadi pada 5,1% subjek (ekspulsi total 4,1% dan parsial 1%) pada 40-42 hari pascasalin dan 7,5% subjek (ekspulsi total 0,6% and parsial 6,9%) setelah 6 bulan pemasangan. Total 9,3% subjek melepas AKDR pada kunjungan pertama dan kedua. Dari seluruh subjek yang melepas AKDR atas permintaan atau mengalami ekspulsi, 61% di antaranya bersedia dipasang ulang. Efektivitas AKDR 100%, dengan 68,9% subjek masih menyusui. Efek samping antara lain keputihan (23%), dismenorea (4-21%), dan perdarahan bercak (2-10%).

Kesimpulan: Penerimaan dan efektivitas AKDR pascaplasenta setelah 6 bulan pemakaian adalah 86,8% dan 100%. Ekspulsi kumulatif sebesar 12,6%, dan efek samping tersering adalah keputihan, dismenorea dan perdarahan bercak.

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Kata kunci: AKDR, efektivitas, ekspulsi, pascaplasenta, penerimaan

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INTRODUCTION

During the postpartum period, the majority of women (92-98%) do not want to get pregnant in 2 months after delivery, based on current world demographics and health surveys. During the postpartum period, 66.5% wants to use contraception in the first year, yet 40% of them does not get contraception care due to many reasons.¹⁻³ Postpartum contraception is the right test period to start contraception use.^{2,3}

Lactational Amenorrhea Method (LAM) as a

postpartum contraception, has resulted 98% in effectiveness if the woman has not have menstruation, exclusive breastfeeding, and the infant age is less than 6 months.²⁻⁵ If LAM requirements are not fulfilled, other effective contraceptive methods are needed.⁴

Progestin hormonal contraception method can be used as a postpartum contraception. However, progestin is a short-term contraception. Implant is a long-term contraception, which is effective for 3-5 years.^{2,6}

IUCD can be applied during the postpartum period, including post-placenta (in 10 minutes after placenta delivery)^{3,5,7-13}, immediate/delayed (in 48 hours until before 6 weeks postpartum)¹⁴ and IUCD after puerperium or interval.^{11-12,15,16} The use of post-placental IUCD is relatively more comfortable, safe, efficient with lower infection incidence^{17,18}, bleeding problem, perforation¹⁵, and expulsion^{9,10,17,19} than immediate or delayed postpartum insertion.¹⁶

Post-placenta IUCD has been introduced since 40 years ago in Indonesia.²⁰ The acceptability of post-placental IUCD Multiload Copper 250 (ML-Cu250), for 3 months of observation, reaches 91.1%.²¹ The effectiveness of post-placental IUCD reaches 2.4% delivery in 1 year.¹⁰ Factors affecting acceptability are expulsion rate and side effects such as bleeding and pain.^{8,11,12} The average of post-placental IUCD expulsion rate ranges cumulatively from 11% through 15% in many countries. In Indonesia, post-placental IUCD expulsion rate is estimated ranging from 6% through 10%.¹⁴ Expulsion rate can be reduced by post-placental insertion, done by experienced installer, and placed precisely in fundus uteri.²²

A previous study in RSCM had been done by Badan Kependudukan dan Keluarga Berencana Nasional (BKKBN). The research interviewed subjects who were inserted IUCD 6 months after delivery. The acceptability was 68% and 26% of the subject removed the IUCD outside RSCM. The most common side effects were lower abdominal pain (40%), and the total expulsion rate was 6 percent.²³

A study about the acceptability, effectiveness, and side effects of post-placental IUCD Cu T380A at RSCM with direct clinical evaluation is an operational study which can be used to support optimal postpartum care in Indonesia generally and to support contraception care in RSCM. Therefore, studies which can show these data are required to be conducted.

METHODS

A prospective study was conducted in the Obstetrics and Gynecology Department, FMUI-RSCM Jakarta during the period of August to October 2012. Patients who met the study criteria were included in the study after signing informed consent. The study protocol had been approved by

the RSCM ethics commission. Inclusion criteria: subjects who were at term pregnancy and scheduled to do vaginal delivery in RSCM, both referral and patient from polyclinic and ward. Subject and partner were willing to participate in the study and chose IUCD as post-placenta contraception method.

Exclusion criteria included presence of uterus anatomic abnormalities, history of menometrorrhagia or dysmenorrhea, history of blood clotting disorders, history of fever or other clinical signs and symptoms that were related to intrauterine or intrapartum infection, history of previous ectopic pregnancy, rupture of the fetal membrane more than 24 hours before hospital admission, delivery which occurred for 24 hours without significant progress and postpartum bleeding.

Subjects who were included in the study would be inserted with IUCD Cu T380A, immediately 10 minutes after placenta were delivered. IUCD was inserted in uterine cavity until it reached fundus with the help of the provider's hand. Providers were Obstetrics and Gynecology FMUI-RSCM residents who were well-trained to do post-placenta IUCD insertion. After insertion, subjects were informed to come in 40-42 days postpartum and 6 months postpartum. Subjects were given a special card to assess bleeding, and to write down address and contact number.

On the next visit, every subject was asked whether there was IUCD which spontaneously expelled, whether she still breastfed, and whether she had gotten her menstrual period. If the patient had got menstruation, patient was asked whether there was any complaint, bleeding, and pain. Patient was also asked whether there was a pregnancy and other complaints were noted. Subject was also asked about satisfaction in using IUCD for 6 months.

Examination using speculum was performed on each subject to assess detached thread from ostium and any other pathology feature in the examination. If IUCD threads were not seen in ostium, the doctor would perform transvaginal USG to ensure the existence of IUCD.

RESULTS

The total number of subjects participating in this study was 234. All subjects were inserted with post-placental IUCD Cu T380A after vaginal

delivery both spontaneously and equipped in RSCM. All subjects were asked and reminded by phone to come in the first re-visit, which was 40-42 days postpartum and 6 weeks postpartum. Subjects who did not come in the first re-visit were re-contacted to come to second re-visit. However, 30 subjects did not come to first and second re-visit, 15 subjects did not come to second re-visit, 19.2% subjects were loss of follow up. There was no statistically significant difference in the characteristics of the subject who came and were loss of follow up.

In patients who removed their IUCD outside RSCM, the most common reasons were presence of the thread which was palpable in the genitalia and vaginal bleeding. IUCD thread could not be seen in 32.6% subjects in the first re-visit and 25% subjects in the second re-visit. Of all the subjects who were both expulsion and removed by request, 8.5% was re-explained and agreed to re-install the IUCD.

There was no pregnancy in any subject for 6 months use of IUCD, 68.9% subjects still breastfed

Table 1. Subjects' Characteristic based on Postplacental IUCD Acceptability

Characteristic	Collectable subjects (n=189)	Loss of follow up (n=45)	p
Age			
Mean (IK 95%)	27.21 (26.36-28.06)	27.11 (25.25-28.97)	0.938 ^a
Median (IQR)	27.00 (22.00-31.00)	27.00 (23.00-31.50)	
Age group			
≤18 years, n (%)	11 (5.8)	3 (6.7)	0.982 ^b
19-25 years, n (%)	67 (35.4)	16 (35.6)	
26-30 years, n (%)	56 (29.6)	14 (31.1)	
31-35 years, n (%)	32 (16.9)	6 (13.3)	
>35 years, n (%)	23 (12.2)	6 (13.3)	
Education			
Non educated, n (%)	1 (0.5)	1 (2.2)	0.982 ^c
Elementary school, n (%)	12 (6.3)	4 (8.9)	
Junior high school, n (%)	48 (25.4)	13 (28.9)	
Senior high school, n (%)	128 (67.7)	27 (60.0)	
Obstetrical status			
Primipara, n (%)	97 (51.3)	24 (53.3)	1.000 ^c
Multipara, n (%)	88 (46.6)	21 (46.7)	
Grande Multipara, n (%)	4 (2.1)	0 (0.0)	

Note:

^aMann-Whitney statistical analysis

^bChi-square statistical analysis

^cKolmogorov-Smirnov statistical analysis

Expulsions occurred in 5.1% subjects (total expulsion rate was 4.1% and partial expulsion rate was 1%) in the 40-42 day visit and 7.5% subjects (total expulsion rate was 0.6% and partial expulsion rate was 6.9%) after 6 months. During the first and second re-visit, 9.3% patients removed IUCD, 2% subjects requested to remove IUCD because they complained pain during sexual intercourse, leukorrhea, and bleeding.

yet 20.1% subjects had not got menstruation. The most common side effects were leukorrhea (23%), menstrual pain (4-21%), and spotting (2-10%). Most of the subjects (45.3-60.1%) had no complaint. Although some patients developed side effects, the majority of the patients were satisfied using post-placenta IUCD Cu T380A. Most of the patients who removed IUCD outside RSCM were not satisfied using IUCD.

Table 2. Six Months Lifetime Table

Variable	N	%
Pregnancy	0	0
Partial expulsion	14	7.9
Total expulsion	9	4.7
Acceptability	164	86.8
Loss of follow up	45	19.2
Total subjects recruited	234	-
Subjects included in this study	189	-

DISCUSSION

As a contraceptive method used during the postpartum period, IUCD has many advantages. Besides, it does not affect breast milk, IUCD is a reversible contraception method and does not need subject compliance to come in the certain time, not depending on the time having sexual intercourse and minimal pain when it was inserted post- partum. Ideal insertion time is 10 minutes after placenta is delivered or in 48 hours after delivery, with higher expulsion rate in the insertion after 48 hours.²⁴

This study was an operational study which studied about post-placenta IUCD Cu T380A which was performed in RSCM. Evaluation was done in 40-42 days and 6 months after insertion. Previous study about post-placenta IUCD, performed follow up in post-puerperial period (40-42 days), 6 months, and 1 year after delivery.^{8-12,24,25}

The acceptability of post-placenta IUCD Cu T 380A until the end of the study was 86.9%. Acceptability of post-placental IUCD in the previous study using IUCD ML Cu 250 was 91.1%²¹, while in the study which was conducted in Turkey compared post-placental insertion, delayed and interval, acceptability of post-placenta IUCD reached. 72.0%²⁶ Lower acceptability compared with previous study which was done follow up for 3 months postpartum was affected by low subject compliance, lack of information which was given in patient education. 7.4% subjects removed IUCD outside RSCM, majority of which due to detached thread complaint (3.2%).

Effectiveness of IUCD for 6 months in this study was 100%. All subjects who used IUCD until the end of the study, there was no one getting pregnant. That number was also affected by breast-feeding activity until 6 months postpartum in

68.9% subjects. Effectiveness of the MAL was 98%.²⁻⁵ Failure rate or pregnancy incidence was less than 1% in the first year use of IUCD. In the long-term study sponsored by WHO, average of the failure rate per year was 0.4% or lower, and cumulative failure rate in 12 years was 2.2%, which was comparable to tube sterilization.¹⁹ In the previous studies, effectiveness after one year use of IUCD was assessed. Further study to assess long-term effectiveness of post-placental IUCD needs to be done.^{8-12,17,24}

Expulsion assessment in this study was obtained 197 from the first re-visit (40-42 days postpartum), 90.4% of subjects IUCD was located fully inside uterine cavity, most of IUCD shifted to cervix in 1% and 4.1% of cases encountered total expulsion. In visit of 6 months IUCD use, 0.6% of cases encountered total expulsion and 6.9% of cases encountered partial expulsion, so that cumulative expulsion rate was 12.6%. Based on the previous study, cumulative expulsion rate after 6 months insertion was, in China 13.3%¹², in Mali 15%⁹, and in Turkey 33.4%.¹⁰

A study conducted in India and Turkey had lower cumulative expulsion rate which were 10.68%²⁴ and 7%.⁸ The most common factors affecting expulsion risks included the experience and expertise of health care provider who performed insertion and insertion technique.¹⁰ In this study, all installers were trained before the study was conducted so that installer ability was considered the same, yet installer experience became factor that needed to consider.

Evaluation of IUCD distance from fundus uteri could be assessed by trans-vaginal USG to determine expulsion objectively. In the study conducted in Brazil, trans-vaginal USG was performed to assess IUCD position in its exact place if IUCD distance was not more than 3 mm from fundus.²⁷ In the next study, it could be evaluated further about exact distance IUCD, by trans-vaginal USG evaluation in each re-visit.

In this study, there was no perforation, one IUCD malposition was occurred in subjects with dyspareunia and reinserted after that IUCD was removed. Numerous multicenter studies found no perforation or infection in post-placental IUCD user.²⁴ In patients whose intrauterine IUCDs were not detected on USG, and from anamnesis the patient did not feel any detached IUCD from genitalia, perforation should be removed by

abdominal x ray examination, which was seldomly performed in this study.²⁴

Infection in puerperal period did not happen in this study. Welkovic et al, stated that 3.4% of IUCD users complained puerperal infection but it was not statistically significant different with subjects not using IUCD.²⁸ Non-itchy and non-stinky leukorrhea as unexpected complaints by the authors was 23.1%. 90% of which still satisfied using IUCD although the complaints existed.

Leukorrhea were not found in IUCD Cu T380A users.²⁵ Eroglu et al stated that leukorrhea complaints which were confirmed by the existence of pathogen were only 1.6% in 6 months postpartum and there was no infection in 8 weeks postpartum in postpartum IUCD insertion.¹⁵ The weakness of this study was no analysis for leukorrhea as complaint, therefore further studies to analyze leukorrhea complaint objectively by finding the pathogens in subject with leukorrhea complaints are needed to be done.

Welkovic found menorrhagia in IUCD users.²⁸ In this study, subjective menorrhagia complaint was 5% and objectively was 2.8% that in the subject's note, bleeding was no more than 5 times changing bandages per day. Thirty three percent of subjects with menorrhagia did not satisfy because of the bleeding. They requested to remove IUCD. Welkovic et al, stated that bleeding and infection after postpartum IUCD insertion were not associated with a lot of bleeding incidence in menstrual cycle.²⁸

In the cumulative side effect assessments, bleeding other than menstruation was spotting subjectively in 15.3% of the subjects and objectively in 4.8% of the subjects. It was because subject did not note properly in the same day. However, 75% of the subjects satisfied using IUCD although there were spotting complaints. All inert IUCD and copper release increased bleeding volume in menstruation when using IUCD, the most possible causes were increase of fibrinolysis activity and local effect on prostacyclin/thromboxane balance in endometrium. New generation IUCD such as Cu T380 and Multiload were reported to cause 50-75% increase in menstrual blood volume.²⁹

CONCLUSION

The acceptability and effectiveness for 6 months were 86.8% and 100%. Expulsion rate side effect for 6 months was cumulatively 12.6%. Other side effects were leukorrhea, menstrual pain, and spotting.

REFERENCES

1. Ross, John A and Winfrey, William L. Contraceptive Use, Intention to Use and Unmet Need During the Extended Postpartum Period. *Int Fam Plan Perspec*, 2001; 27(1): 20-7.
2. Evans A. Postpartum Contraception. *Women's Health Medicine*. The Medicine Publishing Company Ltd. 2005; 25: 23-6.
3. Stephenson P and McDonald P. Family Planning for Postpartum Women: Siezing A Missed Opportunity. *Global Health Technical Briefs*. USAID. 2005: 1-2.
4. Saifuddin AB. Metode Kontrasepsi. *Buku Panduan Praktis Pelayanan Kontrasepsi*. Biran Affandi, Moh. Baharuddin, Soekaemi Soekir, Ed 2. Jakarta: Yayasan Bina Pustaka Sarwono Prawirohardjo, 2010: p. MK-01-88.
5. Farrell B and Huber D. Module 13: Postpartum and Postabortion Contraception. *Comprehensive Reproductive Health and Family Planning, Training Curriculum*. Pathfinder Int; 1998: 6.
6. Centers for Disease Control and Prevention. Update to CDC's US Medical Eligibility Criteria for Contraceptive Use, 2010: Revised Recommendations for the Use of Contraceptive Methods during the Postpartum Period. *MMWR* 2011; 60: 878-83.
7. Ozalp SS. Copper containing, framed intrauterine devices for contraception: RHL commentary (last revised: 15 December 2006). *The WHO Reproductive Health Library*; Geneva: World Health Organization.
8. Celen S, Moroy P, Sucak A, et al. Clinical Outcomes of Early Postplacental Insertion of Intrauterine Contraceptive Devices. *Contracep* 2004; 69(4): 279-82.
9. Morrison C, et al. Clinical Outcomes of Two Early Postpartum IUD Insertion Programs in Africa. *Contracep* 1996; 53(1): 17-21.
10. Eroglu K, Akkuzu G, Vural G, et al. Comparison of Efficacy and Complications of IUD Insertion in Immediate Postplacental/early Postpartum Period with Interval Period: 1 Year Follow-up. *Contracep* 2006; 74(5): 376-81.
11. Kapp N and Curtis KM. Intrauterine Device Insertion During the Postpartum Period: A Systematic Review. *Contracep* 2009; 80(4): 327-36.
12. Xu J-X, Rivera R, Dunson TB, et al. A Comparative Study of Two Techniques Used in Immediate Postplacental Contracep 1996; 54(1): 33-8.
13. Salem HT, Kamel MA, Mohamed SA, et al. Acceptability of Postpartum IUD (PPIUD). *Dept OB/GYN, Faculty of Medicine, Assiut University, Assiut, Egypt* 2004; 6: 21.

14. Saifuddin AB. AKDR Post-Plasenta. Buku Panduan Praktis Pelayanan Kontrasepsi. Biran Affandi, Moh. Baharuddin, Soekaemi Soekir. Ed 2. Jakarta: Yayasan Bina Pustaka Sarwono Prawirohardjo; 2010: p. MK-78.
15. Blanchard H and McKaig C. ACCESS-FP. The IUD: A Contraceptive Option for Postpartum and Postabortion Women. IUD Toolkit. 8 January 2006. <<http://www.k4health.org/toolkits/iud/iud-contraceptive-option-postpartum-and-postabortion-women>>
16. O'Hanley K and Huber DH. Postpartum IUDs: Keys for Success. *Contracep* 1992; 45(4): 351-61.
17. Grimes D, et al. Immediate Post-partum Insertion of Intrauterine Devices. *Cochrane Database Syst Rev* 2003; (1): CD003036.
18. Muller AL, Ramos JGL, Martins-costa SH, et al. Transvaginal Ultrasonographic Assessment of The Expulsion Rate of Intrauterine Devices Inserted in The Immediate Postpartum Period: A Pilot Study. *Contracep* 2005; 72(3): 192-5.
19. Bluestone J, Chase R and Lu ER. Introduction to Intrauterine Contraception Devices. IUD Guidelines for Family Planning Service Programs. Baltimore: JHPIEGO; 2010: 1-12.
20. Soetopo. Pemasangan Dini IUD. Jakarta: Program Studi Obstetri dan Ginekologi, Program Pendidikan Dokter Spesialis-I, Fakultas Kedokteran Universitas Indonesia; 1972.
21. Sitompul E. Penerimaan dan Daya guna AKDR MLCu-250 Pascaplasenta, Hasil Observasi Jangka Pendek. Jakarta: Program Studi Obstetri dan Ginekologi, Fakultas Kedokteran Universitas Indonesia; 1994.
22. The ACQUIRE Project. The Postpartum Intrauterine Device: A Training Course for Service Providers. Participant Handbook. New York: Engender Health. 2008; (6)9: 51-3.
23. Anggraeni M, Asih L dan Pujiastuty R. Operasional Research IUD Post Plasenta di Rumah Sakit Cipto Mangunkusumo (RSCM). Jakarta: Puslitbang KB dan Kesehatan Reproduksi BKKBN, 2010: 27.
24. Shukla M, Qureshi S and Chandrawati. Post-placental Intrauterine Device Insertion - A Five Year Experience at Tertiary Care Centre in North India. *Ind J Med Res* 2012; 136: 432-5.
25. Reinprayoon D, Gilmore C, Farr G, et al. Twelve-months Comparative Multicenter Study of The TCU380A and ML 250 Intrauterine Devices in Bangkok, Thailand. *Contracep* 1998; 58(4): 201-6.
26. Hasson HM, Copper IUDs. *J Reprod Med* 1978, 20:139-54.
27. Petta CA, Faundes D, Pimentel E et al. The Use of Vaginal Ultrasound to Identify Copper T IUs at High Risk of Expulsion. *Contracep* 1996; 54: 287-9.
28. Welkovic S. Post-partum Bleeding and Infection after Post-placental IUD Insertion. *Contracep* 2001; 63(3): 155-8.
29. Odland V. Modern Intra-uterine Devices. Bailliere's Clinical Obstetrics and Gynaecology. Bailliere Tindall; 1996. <<http://www.ncbi.nlm.nih.gov/pubmed/8736722>>

Research Article

The Association of Bladder Wall Thickness with Severity of Symptoms in Patients with Overactive Bladder

Hubungan antara Ketebalan Dinding Vesika Urinari dengan Keparahan Gejala pada Pasien Overactive Bladder

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Abstract

Objective: To investigate the association of bladder wall thickness (BWT) with severity of symptoms in overactive bladder patients in Obstetrics and Gynecology Department Dr. Mohammad Hoesin general hospital Palembang.

Methods: An analytical observational study was conducted at Gynecology clinic Dr. Mohammad Hoesin General Hospital Palembang from November 2015 to August 2016. Data were analyzed with SPSS 16.0 for Windows. Bivariate analysis with the Chi square and association Rank-Spearman test was used to assess the association between BWT and visual analog scale (VAS).

Results: Fourty subjects were included in the study. The mean BWT in the overactive bladder group was thicker compared to those without overactive bladder (5.8522 ± 0.5783 vs 5.2176 ± 0.67937). There was significant association between BWT and overactive bladder complaints. Abnormal group ($\geq 5\text{mm}$) had 12 times risk of overactive bladder compared to normal sample ($\leq 5\text{mm}$) ($p = 0.029$, $RR = 12$).

Conclusion: Thus, the thickness of the urinary bladder wall measured with ultrasound examination (USG) can be used to assess the status and degree of urinary disorders in women with complaints of painful urinate and urinary disorders.

[Indones J Obstet Gynecol 2017; 5-4: 219-224]

Keywords: bladder wall thickness, detrusor overactivity, overactive bladder, visual analog scale

Abstrak

Tujuan: Menilai hubungan ketebalan dinding vesika urinaria dengan Visual Analog Scale (VAS) pada penderita gangguan berkemih di Departemen Obstetrik dan Ginekologi RSUP Dr. Mohammad Hoesin Palembang.

Metode: Studi observasional analitik telah dilakukan di poliklinik Ginekologi RSUP Dr. Mohammad Hoesin Palembang dari November 2015 sampai Agustus 2016. Sebanyak 40 subjek penelitian yang memenuhi kriteria inklusi dimasukkan dalam penelitian. Data dianalisis dengan menggunakan program SPSS 16.0 dan dilakukan analisis bivariat dengan chi-square dan uji korelasi Rank-Spearman untuk menilai korelasi ketebalan dinding vesika urinaria dengan visual analog scale (VAS).

Hasil: Studi menunjukkan rerata ketebalan dinding vesika urinaria kelompok gangguan berkemih lebih tebal dibanding kelompok tanpa gangguan berkemih ($5,8522 \pm 0,5783$ vs $5,2176 \pm 0,67937$). Terdapat hubungan bermakna antara kategori ketebalan dinding vesika urinaria dengan keluhan gangguan berkemih, di mana kelompok sampel dengan tidak normal ($\geq 5 \text{ mm}$) berisiko 12 kali mengalami gangguan berkemih dibanding kelompok sampel dengan BWT normal ($\leq 5\text{mm}$) ($p = 0,029$, $RR=12$).

Kesimpulan: Sehingga ukuran tebal dinding vesika urinaria dari hasil pemeriksaan (USG) dapat digunakan untuk menilai status dan derajat gangguan berkemih pada perempuan dengan keluhan nyeri dan gangguan berkemih.

[Maj Obstet Ginekol Indones 2017; 5-4: 219-224]

Kata kunci: detrusor overactivity (DO), ketebalan dinding vesika urinaria (BWT), gangguan berkemih, skala visual analog

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INTRODUCTION

Overactive bladder (OAB) is a common urinary condition characterized by urinary urgency with or without urinary incontinence, frequent urination (the need to urinate 8 times or more in a period of 24 hours), and nocturia (waking up at night to urinate twice or more). The International Continence Society (ICS) is defined overactive

bladder as a syndrome, consist in go furinary urgency with or without incontinence, usually accompanied with frequent urination and nocturia.^{1,2}

A study conducted in England found that the overall prevalence of OAB in the general population was 12%. This figure is roughly the same with other countries. Generally, the

incidence of overactive bladder is approximately 20 to 40% of all urinary incontinence. Using urodynamic examination in patients with urinary incontinence, overactive bladder is found in about 24.4% cases, and this number keeps increasing with age. Previous studies show that 75% of male patients with urge incontinence and 44% of male patients with urinary frequency have detrusor overactivity (DO). A previous study conducted on 44% of women, 54.2% of patients with the symptoms of urinary disorders have a DO. However, these studies were carried out before the new ICS report was published. Thus, it was based on the old definition of urgency.¹⁻⁴

Symptoms of urinary disorders include urinary frequency as much as 8 times or more in one day, or 1 time or more during the night; urgency to urinate which occurs suddenly, a strong desire to urinate immediately; urge incontinence, which is the inability to resist the urge to urinate. These symptoms may lead to various problems such as impaired physical activity and work, social interaction, psychological problems (depression), impaired sleep patterns, and sexual problems-all of which is a disruption to the quality of life.³⁻⁵

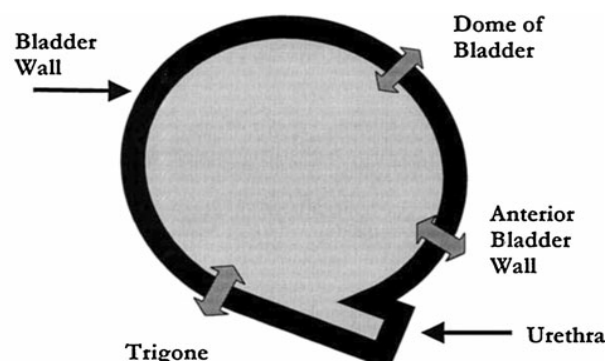
Some researchers have been working to find other diagnostic methods that are cheaper, easier, non-invasive, and reliable. Ultrasonography (USG) was found to meet these criteria, coupled with the advantage of not requiring the use of contrast material and X-ray exposure. USG is proven to be useful to evaluate urethro-vesical junction in stress urinary incontinence and may estimate the post-voiding residual volume. Measuring of bladder wall thickening with transvaginal ultrasound is expected to aid in diagnosing women with detrusor overactivity as well as those with stress urinary incontinence (SUI).^{6,7}

In a study of 247 women with overactive bladder symptoms, Serati et al. (2010) found that BWT values in women with DO, measured using transvaginal ultrasound were significantly higher ($p < 0.0001$). They used a cut-off of 5.0 mm with a positive predictive value of 100%. Panayi et al. (2010) conducted a study on 378 women with the average age of 56 years old, and concluded that the mean BWT is associated with symptoms of urinary disorders and mixed urinary incontinence (MUI), higher urination frequency of urination during the day and night, and greater visual analog scale (VAS). Detrusor overactivity is characterized by

involuntary bladder-muscle contraction. Continuous contraction of detrusor muscle may led to thickening of the bladder wall. Thickening of the bladder wall will subsequently induce the sensation of pain caused by the decrease in bladder capacity, and urinary disorders characterized by frequency, nocturia, and urgency. Therefore, it is post-lated that there is a association between bladder wall thickness and a higher visual analog scale in overactive bladder patients. This study was proposed to test this association in Dr. Mohammad Hoesin Hospital Palembang, where a research on the association of BWT and VAS in patients with overactive bladder at Dr. Mohammad Hoesin Hospital Palembang or in South Sumatera has never been done before.⁸⁻¹¹



Figure 1. Transvaginal scan of the normal bladder wall showing measurements of the trigone and parts of the dome From Panayi.¹²



Mean Bladder Wall Thickness	=	$\frac{\text{Dome} + \text{Anterior Wall} + \text{Trigone}}{3}$
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Figure 2. Bladder wall thickness From Panayi¹²

METHODS

This was a cross sectional study conducted at the gynecologic clinic of Dr. Mohammad Hoesin Hospital, Palembang, Indonesia. The data was gathered starting from November 2015 until August 2015.

Subjects were women with overactive bladder symptoms. The total sample in this study were 40 patients, which consisted of 17 controls and 23 cases. Data were analyzed using SPSS 16.0 and bivariate analysis using Chi-square and Spearman Rank association test were conducted to assess the association of BWT with VAS.

RESULTS

Mean BWT was thicker in the group with urinary disorders compared to those without urinary disorders (5.8522 ± 0.5783 vs 5.2176 ± 0.67937). Table 1 shows the characteristics of the study subjects at the time of data collection. It appears that urinary disorders mostly occur at a young age (<40 years) (65.2%), on highly educated women (high school graduation) (47.8%), women with ideal BMI (52.2%), multiparous women (47.8%), women with no history of CS or abortion (4.3%), women with abnormal BWT (95.7%), and all complained of painful urination (100%). There was no significant difference in the characteristics of samples with and without urinary disorders, showing that the demographic characteristics bias has been successfully minimized in this study.

Table 1. Demographic Characteristics

Variable	Urinary disorders (+) (N=23)		Urinary disorders (-) (N=17)	
	n	%	n	%
Age				
Young	15	65.2	8	47.1
Elders	8	34.8	9	52.9
Residence				
Urban area	11	47.8	8	47.1
Rural area	12	52.2	9	52.9
Education				
Un educated	1	4.3	0	0
Elementry school	3	13	3	17.6
Junior school	4	17.4	2	11.8
High school	11	47.8	9	52.9
University	4	17.4	3	17.6

BMI

Underweight	4	17.4	0	0
Ideal	12	52.2	10	58.8
Overweight	4	17.4	3	17.6
Obese	3	13	4	23.5

Parity

Nullipara	9	39.1	7	41.2
Primipara	3	13.1	4	23.5
Multipara	11	47.8	6	35.3

History of CS

CS (-)	22	95.7	17	100
CS (+)	1	4.3	0	0

History of abortion

(-)	22	95.7	16	94.1
(+)	1	4.3	1	5.9

BWT category

Normal	1	4.3	6	35.3
Abnormal	22	95.7	11	64.7

Painful urination

Not Pain	0	0	1	5.90
Mild Pain	19	82.6	11	82.4
Moderate Pain	3	13	2	11.8
Severe Pain	1	4.3	0	0

Table 2. Association between Urinary Disorders and Bladder Wall Thickness (BWT)

BWT category	Urinary disorder	normal urinary	p	RR
	n	n		
Abnormal (≥ 5 mm)	22	11	0.029	12
Normal (≤ 5 mm)	1	6		
Total	23	17		

Fisher exact test, $p < 0.05$.

Table 2 shows significant association between BWT categories and complaints of urinary disorders, where the sample group with abnormal BWT (> 5 mm) has risk of experiencing urinary disorders 12 times higher compared to the group with normal BWT (< 5 mm) ($p = 0.029$, $RR = 12$).

Figure 3 shows significant association ($p = 0.001$, $R = 0.269$) between BWT with a total OABSS, where the thicker the bladder wall, the greater the urinary disorders.

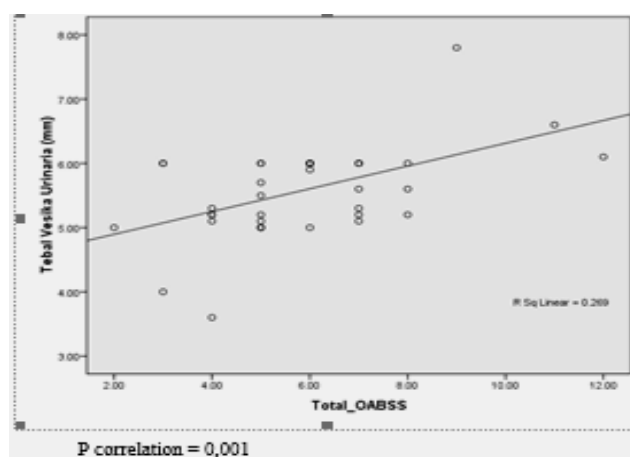


Figure 3. Association between BWT and total OABSS.

Table 3. Association between Pain during Urination and Category of BWT

BWT category	VAS moderate-severe pain	VAS no pain-mild pain	p
	n	n	
Abnormal ($\geq 5\text{mm}$)	6	27	0.567
Normal ($\leq 5\text{mm}$)	0	7	
Total	6	34	

p association < 0.001

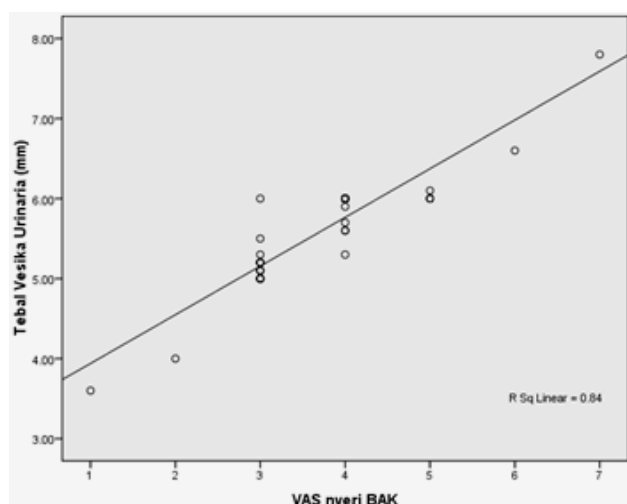


Figure 4. A graph of association between BWT and VAS of urinating pain.

Figure 4 shows significant association ($p < 0.001$, $R = 0.84$) between the BWT and painful urination measured in VAS, where the thicker the bladder wall, the more severe the pain. The difference in the significance of findings between the association

analysis and association on variable voiding BWT and VAS pain may be due to categorical bias, where the numerical variables are much more representative than categorical data that may lead to biased categorization. Thus, it can be concluded that there is a significant association between these two variables.

Table 4. Association between Painful Urination and Urinary Disorders

Urinary disorders	VAS moderate-severe pain	VAS no pain-mild pain	p
	n	n	
Impaired	4	19	0.489
Normal	2	15	
Total	6	34	

Fisher exact test, $p < 0.05$

P value = 0.001

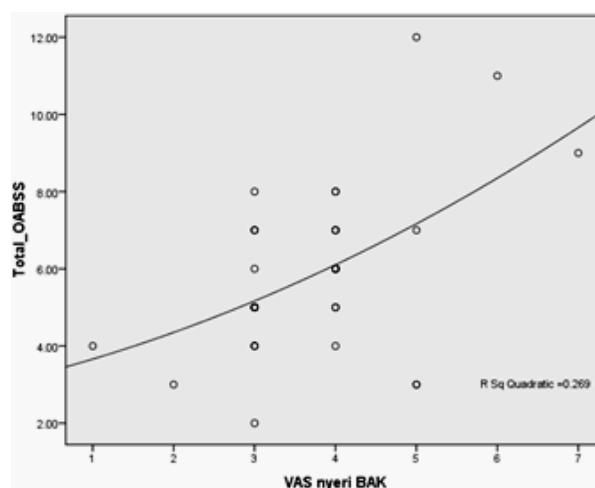


Figure 5. A graph of association between total OABSS and painful urination measure in VAS.

Figure 5 shows that there is a weak, yet significant association ($p = 0.001$, $R = 0.269$) between urinary complaints and the VAS of urinating pain, where the higher the total OABSS, the more severe the urinating pain.

The difference in the significance of findings between association analysis and the association between the variables of total OABSS and VAS of urinating pain may be caused by categorical bias, where the numerical variables are much more representative than the categorical data which may lead to biased categorization. Thus, it can be concluded that there is a significant association between these two variables.

DISCUSSION

In this study, the diagnosis of urinary disorders/OAB is established based on OABSS (overactive bladder Symptom Score) criteria, where the patients complains of urinary frequency $>8x/day$, signs of urgency, and nocturia $>1x/day$. The frequency of each symptom was determined by the patient herself and was acquired from the VAS questionnaire.¹²⁻¹⁴

We found that urinary disorder occurs more often in women with young age (62.5%). This finding is contradictory to the existing theory, where old age causes a decrease in pelvic floor muscle function and a higher risk of developing urinary disorders, especially OAB. However, Dwyer et al. (2002) and Telokan et al. (2006) found no significant association between age and the incidence of urinary disorders, especially OAB.¹⁵

Statistical analysis found a significant association between BWT with urinary disorders, where in women with BWT $\geq 5mm$ have 12x the risk of experiencing urinary disorders compared to those with BWT ≤ 5 mm. This finding is consistent with the theory in which repetitive involuntary contractions of the bladder muscle, the pathophysiology of OAB, against the closed sphincter will over time cause hypertrophy of the detrusor muscle (secondary impact) and manifests as the bladder wall thickening (BWT) on ultrasound examination. Nevertheless, analysis association found a weak positive association between BWT and urinary disorders. This may be due to the small and uneven sample size (majority of the samples have BWT ≥ 5 mm).¹⁶

Spearman who association analysis found a significant association between the BWT and the VAS of urinating pain. This is similar to a study by Panayi et al. (2010), and it may be concluded that BWT may reflect the severity of urinary disorders experienced by the respondents. Shu Yu and Panayi found similar findings to those in this study. However, the cause of the bladder wall thickening, as hypothesized by Shu Yu, may be caused by inflammation or obstruction, two things that have yet to be controlled by the researchers in this study. When bladder wall thickening is caused by inflammatory process, in addition to the findings of urinary disorders, a complaint of pain during urination will also be significant. However, if the thickening is caused by a chronic obstruction, the urinating complaint may not be significant.^{16,17}

Similar to the earlier discussion of BWT's association with VAS of urinating pain, a significant positive association was also found between the VAS of micturition pain and urinary disorders. From this finding, it can then be concluded that the VAS of micturition pain is a reflection of the degree of urinary disorders, measured in a total OABSS score. Weak association of these two variables seems to be an uncommon finding. Considering the strong association between BWT and VAS, the association between VAS and urinary disorders should also be strong. VAS of micturition pain is a different variable from VAS of the urinary disorders and is a reflection of "pain" during urination, and so, is highly subjective in each individual, especially if there are other conditions that may increase the pain (such as urinary tract infections, post partum, trauma, etc.), which in this study has yet to be controlled. Thus, it is understandable that this unusual findings may be due to two main causes: 1) the respondent bias (value of VAS of the micturition pain is highly subjective) and 2) there is no direct association between urinary disorders (total OABSS score) and VAS of micturition pain, and so the association between VAS of micturition pain and urinary disorders is assumed to be similar to the association between VAS of micturition pain and BWT.¹⁸⁻²⁰

This research is a pioneer study assessing the association between BWT and urinary problems in Asian societies, and particularly Indonesia. In contrast to research Panayi et al. (2010) which addressed the European population. Researchers did a direct assessment using a questionnaire (primary data) in establishing the diagnosis of urinary disorders. Ultrasound examination was carried out by consultants who are competent in the field of ultrasound.

This research itself also has some crucial drawbacks: urinary tract infections that may cause OAB and aggregate painful urination were not controlled in this study; the small sample size; and the value of BWT, in particular, which is not normally distributed (the majority of sample was in the ≥ 5 mm group) may cause the analysis to be biased because of the unequal distribution of numerical variables.

Nevertheless, the result of this study is expected to contribute the understanding of the pathophysiology of urinary disorders, especially in terms of anatomy of the bladder, and may become an

invasive and inexpensive predictor tool in assessing the degree of urinary disorders.

CONCLUSIONS

BWT is associated with urinary disorders and painful urination. The thicker the bladder wall, the greater the degree of urinary disorders and micturition pain. Thus, the size of the BWT measured with ultrasonography examination (USG) can be used to assess the status and degree of urinary disorders in women with complaints of pain and urinary disorders.

REFERENCES

1. Ouslander JG. Management of overactive bladder. *NEJM*. 2004; 350.8: 786-99.
2. Irwin J, Debra E. Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. *BJU Int*. 2006; 97:1 96-100.
3. Junizaf, Santoso BI. Buku Ajar Uroginekologi Indonesia. Himpunan uroginekologi Indonesia. Jakarta. 2011
4. Kelleher Con MJ. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. *BJU Int*. 2005; 95.1: 81-5.
5. Nitti V, Taneja S. Overactive bladder: achieving a differential diagnosis from other lower urinary tract conditions. *Int Clin Pract*. 2005; 59.7: 825-30.
6. Yamaguchi O. Defining clinical assessment in overactive bladder. *Int Clin Pract*. 2004; 58.s140: 4-5.
7. Cardozo L. The overactive bladder syndrome: treating patients on an individual basis. *BJU Int*. 2007; 99.s3: 1-7.
8. Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol*. 2006;175.1: 191-4.
9. Dmochowski R. Evaluating the effectiveness of therapies for urinary incontinence. *Reviews in urology*. 2001; 7-14.
10. Farag FF, Haesakkers JP. Non-invasive techniques in the diagnosis of bladder storage disorders. *Neurol Urodynamics*. 2011; 30: 1422-8.
11. Haylen BT, Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, et al. Int Urogynecol Association (IUGA)/Int Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol*. 2010; 21: 5-26.
12. Panayi DC, Khullar V, Fernando R, Tekkis P. Transvaginal ultrasound measurement of bladder wall thickness a more reliable approach than transperineal and transabdominal approaches. *BJU Int*. 2010; 106 : 1519-22.
13. Rachaneni S, Balogun M, Latthe P. Bladder-wall-thickness ultrasound scan in the investigation of LUTS in women: challenges and limitations. *Int Urogynecol J*. 2013; 24: 725-8.
14. Fujihara A, Ukimura O, Honjo H, Iwata T, Ueda T, Matsugami T, et al. Urge perception index of bladder hypersensitivity. *J Urogynecol*. 2013; 189: 1797-803.
15. Panayi DC, Tekkis RF, Hendricken C, Khullar V. Ultrasound measurement of bladder wall thickness is associated with the overactive bladder system. *Neurol Urodynamics*. 2010; 29: 1295-8.
16. Lekskulchai O, Dietz HP. Detrusor wall thickness as a test for detrusor overactivity in women. *Ultrasound Obstet Gynecol*. 2008; 32: 535-9.
17. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline. *Am Urol Association Edu Research, Inc*. 2012;188(supp 6):2455-63.
18. Wennberg AL, Altman D, Lundholm C, Klint A, Iliadou A, Peeker R, et al. Genetic Influences Are Important for Most But Not All Lower Urinary Tract Symptoms: A Population-Based Survey in a Cohort of Adult Swedish Twins. *Eur Urol*. 2011; 59(6): 1032-8.
19. Palma T, Raimondi M, Souto S, Fozzatti C, Palma P, Riccetto C. Association between body mass index and overactive bladder symptoms in pre-menopausal women. *Rev Assoc Med Bras* 2014; 60(2): 111-7.
20. Wu SY, Jhang JF, Jiang YH, Kuo HC. Increased bladder wall thickness is associated with severe symptoms and reduced bladder capacity in patients with bladder pain syndrome. *J Urol*. 2015; 6: 154.

Research Article

The Degree of Cystocele and Rectocele with Hiatal Area Levator Ani

Derajat Cystocele dan Rectocele dengan Hiatal Area Levator Ani

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Abstract

Objective: To investigate the degree of cystocele and rectocele with a maximum of levator hiatal area (AHL) during Valsava.

Methods: Secondary data analysis of 90 patients with uterine prolapse January 2012 to November 2013 in the clinic Urogine-kologi RSCM, Jakarta. 3D/4D ultrasound measurement and pelvic organ prolapse system Quantification (POP-Q) stage I-IV cystocele and rectocele stage I-IV. All statistical analyses were analyzed using Stata 20 for Windows.

Results: Significant difference cystocele stage I-II ($n = 25$) with stage III-IV ($n = 65$), the maximum AHL with a difference of 4.33 cm^2 ($p = 0.040$). In rectocele stage I-II ($n = 64$) and stage III-IV ($n = 26$) of 3.85 cm^2 ($p = 0.130$). AUC values for stage I-II and III-IV cystocele was 0.607 (IK95% from 0.467 to 0.738), and the ROC for rectocele was 0.603 (IK95% from 0.472 to 0.734). The ROC optimal cut point for cystocele stage I-II with III-IV with the highest sensitivity and specificity is 29 cm^2 (sensitivity 0.523 , specificity 0.520), the rectocele is 30 cm^2 (sensitivity 0.538 , specificity 0.584).

Conclusion: There is a significant relationship between the degree of cystocele and area of the levator ani muscles when Valsava, but there is no relationship at rectocele. The value of maximum area under the curve (AUC) hiatal area of the levatorani muscle in distinguishing stage I-II and III-IV cystocele are relatively similar to rectocele stage I-II and III-IV. Optimal cut point hiatal area of the levatorani muscle in distinguishing stage I-II and III-IV cystocele is 29 cm^2 , while for rectocele is 30 cm^2 with sensitivity and specificity values were quite good.

[Indones J Obstet Gynecol 2017; 5-4: 225-229]

Keywords: cystocele, levatorani hiatal area, pelvic organ prolapse, rectocele

Abstrak

Tujuan: Mengetahui derajat sistokel dan rektokel dengan maksimal area hiatal levator (AHL) saat Valsava.

Metode: Analisa data sekunder 90 pasien prolaps uteri Januari 2012 hingga November 2013 di poliklinik Uroginekologi RSCM, Jakarta. Pengukuran ultrasonografi 3D/4D dan pelvic organ prolapse quantification system (POP-Q) sistokel derajat I-IV dan rektokel derajat I-IV. Dianalisis dengan stata program 20 for windows.

Hasil: Perbedaan bermakna sistokel derajat I-II ($n=25$) dengan derajat III-IV ($n=65$), maksimal AHL dengan perbedaan sebesar $4,33 \text{ cm}^2$ ($p=0,040$). Pada rektokel derajat I-II ($n=64$) dan derajat III-IV ($n=26$) sebesar $3,85 \text{ cm}^2$ ($p=0,130$). Nilai AUC untuk sistokel derajat I-II dengan III-IV adalah $0,607$ (IK95% $0,467 - 0,738$), untuk rektokel adalah $0,603$ (IK95% $0,472 - 0,734$). Titik potong optimal ROC untuk sistokel derajat I-II dengan III-IV dengan sensitivitas dan spesifitas tertinggi adalah 29 cm^2 (sensitivitas $0,523$, spesifitas $0,520$), pada rektokel adalah 30 cm^2 (sensitivitas $0,538$, spesifitas $0,584$).

Kesimpulan: Terdapat hubungan bermakna antara derajat sistokel dengan area hiatal otot levator ani saat valsava, namun tidak terdapat hubungan pada rektokel. Nilai area under curve maksimal area hiatal otot levator ani dalam membedakan sistokel derajat I-II dan III-IV relatif sama dengan rektokel derajat I-II dan III-IV. Titik potong optimal area hiatal otot levator ani dalam membedakan sistokel derajat I-II dan III-IV adalah 29 cm^2 , sedangkan untuk rektokel adalah 30 cm^2 dengan nilai sensitivitas dan spesifitas yang cukup baik.

[Maj Obstet Ginekol Indones 2017; 5-4: 225-229]

Kata kunci: area hiatal levator ani, prolaps organ panggul, rektokel, sistokel

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INTRODUCTION

Levator ani muscle plays an essential role in holding pelvic organs. Impairment to the structure of this muscle may result in pelvic organ prolapse, particularly in the middle and anterior compartment.^{1,2} Prolapse of the anterior vaginal wall may occur due to weakness of the connective tissue and pubocervical fascia, which subsequently may involve bladder, which is known as cystocele, while

the posterior wall prolapse may involve lower rectum, which is named as rectocele. Measurement of the area of levator ani hiatus is essential for predicting the occurrence of pelvic organ prolapse for women in the future, so that the potential occurrence of pelvic organ prolapse can be prevented early.^{3,4}

A study at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, in 2014 found a significant

association between the degree of uterine prolapse and the area levator ani hiatus. Further studies providing the data on the relationship degree cystocele and rectocele with levator hiatal area when the Valsalva maneuver. This study will also determine the maximum Area Under the Curve (AUC) levator hiatal area when the Valsalva maneuver to distinguish degrees of cystocele and rectocele. So in this study will be known relationship between the degree cystocele and rectocele with the size of the levatorani hiatal area.

Pelvic organ prolapse (POP) is anatomically defined as downward descent of pelvic organs into or through the vagina, perineum or anal canal. POP occurs due to impairment of the structural support and the mounting of the uterus and vagina.⁵ Prolapse of the anterior vaginal wall caused by weakness of the pelvic advocates may lead to cystocele. Symptoms often found on the anterior vaginal wall prolapse are frequency, urgency, intermittent urinary flow, straining during urination, incomplete bladder emptying and urine flow is not smooth.^{6,7} Posterior vaginal wall prolapse is caused by rectovaginal septal defect. This is known as rectocele. Several symptoms found in the posterior vaginal wall prolapse is strong straining during defecation, incomplete defecation, constipation, as well as manual evacuation digitally by exerting pressure on the perineum or vagina.⁸

Damage to the levator ani muscles will cause avulsion or overdistention of the levator ani, while damage to the neuromuscular will decrease levator ani tone. This will subsequently lead to the widespread area of the levator ani hiatus which in turn will lead to uterine prolapse, cystocele and

rectocele.^{9,10} Damage and weakness of endopelvic fascia and vaginal wall will directly lead to uterine prolapse, cystocele, and rectocele. Several things including spontaneous labor or assisted vaginal delivery, macrosomia, prolonged second stage, extensive perineal tears, menopause, obesity, increased intra-abdominal pressure.¹¹

METHODS

This was a cross-sectional study. This study was conducted at the Department of Obstetrics and Gynecology of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia during the period of May to June 2016. The medical records of patients diagnosed with uterine prolapse who went to the Urogynecologic Clinic of Dr. Cipto Mangunkusumo Hospital between January 2012 and November 2013 were evaluated. All statistical analyses were analyzed using Statistics Data Analysis 20 (Stata 20).

RESULTS AND DISCUSSION

A total of 90 subjects were recruited in this study. There were significant differences for the age of the patients in both groups. Patients with stage I-II cystocele were younger compared to the those with stage III-IV cystocele (54.64 ± 13.35 vs 59.71 ± 9.40). This is consistent with a previous study by Patel et al¹² which suggested that age was the main risk factor for the occurrence of primary POP. However, older age at delivery has not showed a clear correlation with the incidence of the primary POP. Those with older age was also associated with menopausal condition seen in this study. The prevalence of cystocele occurs more frequently in

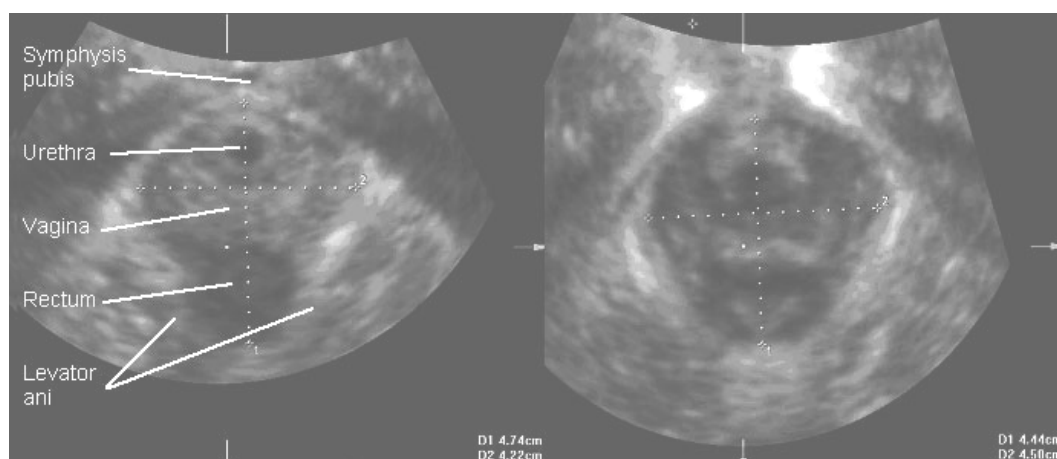


Figure 1. Levator hiatus during relaxation (left) and Valsalva maneuver (right)

women who were in the postmenopausal state. Total parity was not associated with the incidence of POP in this study. This is contrast with a previous study conducted by Vergeldt et al.¹³ This difference may occur due to the distribution of the data subject of different studies, where the number of patients with a high degree of prolapse number were three times higher compared to the those with low degree prolapse. The baby's weight is also no effect on the incidence of cystocele and rectocele in the study sample. Vaginal delivery and parity was a risk factor that is often done research on the occurrence of cases of primary POP.¹⁴ The use of tools when parturition associated with a lower risk of developing high degree cystocele and rectocele III-IV in this study. These results are consistent with studies by Glazener which investigated the incidence of cystocele, rectocele and avulsion with the use of tools when parturition at 726 subjects.¹³

There was a significant difference between the maximum value of the area of levator ani hiatus during Valsava maneuver. The maximum value of the area of the levator ani hiatus on stage I-II cystocele was $28.45 + 7.82 \text{ cm}^2$ lower than the hiatal area levatorani cystocele stage III-IV is $32.78 + 10.98 \text{ cm}^2$. These results are consistent with previous studies by Vergeldt et all and Dietz.⁷ In those with rectocele, there were no found significant differences of the maximum value of the area of the levator ani hiatus. The results obtained in the different groups of rectocele with existing literature were due to the differences in sample size and distribution of the samples in this study. In this study, the results obtained were not statistically significant.¹³

The value of AUC obtained for groups of cystocele was 0.607 (CI 95% from 0.467 to 0.738), which means the ability of discrimination in a category is, for groups rectocele obtained 0.603 (CI 95% from 0.472 to 0.734), which means the ability of discrimination in a category is, Results of statistical analysis, the best cut point to be limits in distinguishing low incidence and high degree cystocele is 29 cm^2 . For the cut-off point, the value of 0.523 was good enough. The sensitivity and specificity value is 0.520, while for rectocele is 30 cm^2 , with a 0.538 value of sensitivity and specificity values 0.584.

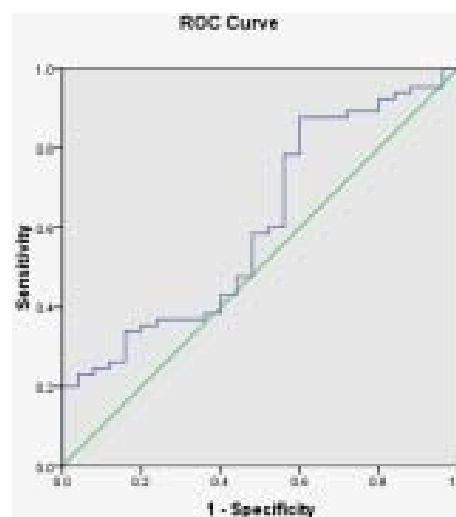


Figure 2. ROC curve mask AHL group cystocele stage I-II and III-IV

Table 1. Comparison of the Max Value of the AHL on Cystocele Group Stage I-II and III-IV

Cystocele	N	Average +SD (cm ²)	Mean difference (CI 95%)	p
Stage I-II	25	28.45+7.82	4.33 (-0.20- 8.46)	0.040
Stage III-IV	65	32.78+10.98		

Table 2. Comparison of the Max Value of the AHL in Group Rectocele Stage I-II and III-IV

Cystocele	N	Average +SD (cm ²)	Mean difference (CI 95%)	p
Stage I-II	64	30.47+9.80	3.85 (-1.19- 8.89)	0.130
Stage III-IV	26	34.32+11.10		

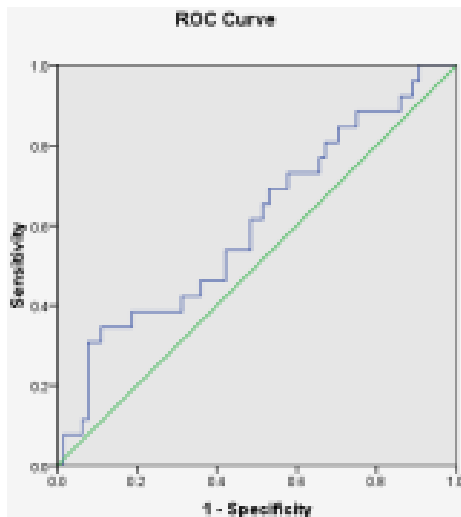


Figure 3. ROC curve max AHL rectocele group stage I-II and III-IV

Table 3. Assessment of Sensitivity and Specificity to Distinguish Max AHL Group Cystocele Stage I-II and III-IV at some Cut Point

Cut Point	Sensitivity	Specificity
24	0.800	0.400
24.5	0.785	0.400
25	0.785	0.440
25.5	0.769	0.440
26	0.708	0.440
26.5	0.631	0.440
27	0.600	0.440
27.5	0.600	0.440
28	0.585	0.480
28.5	0.554	0.480
29	0.523	0.520
29.5	0.508	0.520
30	0.477	0.520
30.5	0.477	0.520

Table 4. Assessment of Sensitivity and Specificity to Distinguish Max AHL group Rectocele Stage I-II and III-IV at some Cut Point

Cut Point	Sensitivity	Specificity
23	0.877	0.380
23.5	0.877	0.400
24	0.815	0.400
24.5	0.785	0.400
25	0.785	0.440

25.5	0.769	0.440
26	0.692	0.440
27	0.692	0.484
27.5	0.692	0.484
28	0.654	0.484
28.5	0.615	0.512
29	0.577	0.512
29.5	0.538	0.512
30	0.538	0.584
30.5	0.500	0.584

CONCLUSION

The degree of cystocele is associated with area of the levator ani hiatus during Valsava maneuver. However, there is no association between the degree of rectocele and area of levator ani hiatus during Valsava. The value of AUC maximum area of the levator hiatus muscle in distinguishing stage I-II and III-IV cystocele are relatively similar to stage I-II and III-IV rectocele.

REFERENCES

- Clark NA BC, Yousef A, DeLancey JOL. Levator defects effect perineal position independently of prolaps status. *Am J Obstet Gynecol.* 2010; 203(6): e17-e22.
- Durnea CM KA, Kenny LC, Durnea UA, Smyth MM, O'Reilly BA. Prevalence, etiology and risk factors of pelvic organ prolapse in premenopausal primiparous women. *Int Uro-gynecol J.* 2014; 25: 1463-70.
- Laila Najjari JH, Pia Larscheid, Thomas Papathemelis, and NicolaiMaass. Perineal Ultrasound as a Complement to POP-Q in the Assessment of Cystoceles. *Bio Med Research Int.* 2014: 1-8.
- Schettino MT DE, Rossi C, Panariello A, Vascone C, Coppola G, Iervolino SA, Assisi DD, Mainini G, Torella M. Possible role of perineal ultrasound in the diagnosis of cystocele. *Clin Exp Obstet Gynecol.* 2015; 42: 321-6.
- Shek KL DH. The effect of childbirth on hiatal dimensions. *Obstet Gynecol.* 2009; 113: 1272-8.
- Barber MD MC. Epidemiology and outcome assessment of pelvic organ prolapse. *Int Urogynecol J.* 2013; 24: 1783-90.
- Dietz HP HK, Wong V. The natural history of cystocele recurrence. *Int Urogynecol J.* 2014; 25: 1053-7.
- Collins SA1 OSD, Lasala CA. Correlation of POP-Q posterior compartment measures with defecatory dysfunction. *Int Urogynecol J.* 2012: 23.
- Dietz HP FA, Shek KL, Kirby A. Avulsion injury and levator hiatal ballooning: two independent risk factors for prolapse? An observational study. *Acta Obstet Gynecol Scand.* 2012; 91: 211-4.
- Abdool Z SK, Dietz HP. The effect of levator avulsion on hiatal dimension and function. *Am J Obstet Gynecol.* 2009; 201: 89e1-5.

11. de Landsheere L BS, Munaut C, Nusgens B, Rubod C, Noel A, Foidart JM, Cosson M, Nisolle M. Changes in elastin density in different locations of the vaginal wall in women with pelvic organ prolapse. *Int Urogynecol J*. 2014; 25: 1673-81.
12. Patel DA, Xu X, Thomason AD, Ransom SB, Ivy JS, Delancet JO. Childbirth and pelvic floor dysfunction: an epidemiologic approach to the assessment of prevention opportunities at delivery. *Am J Obstet Gynecol*. 2006; 195: 23-8.
13. Vergeldt TFM, Weemhoff M, IntHout J, Kluivers KB. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. *Int Urogynecol J*. 2015; 26(11): 1559-73.
14. Glazener C, Elders A, Macarthur C, Lancashire RJ, Herbison P, Hagen S, Dean N, Bain C, Tooze-Hobson P, Richardson K, McDonald A, McPherson G, Wilson D. Childbirth and prolapse: long-term associations with the symptoms and objective measurement of pelvic organ prolapse. *BJOG*. 2013; 120(2): 161-8. doi: 10.1111/1471-0528.12075.

Research Article

Radiotherapy Response of Cervical Cancer Patients at a Tertiary Referral Hospital in Indonesia

Respon Terapi Radiasi Pasien Kanker Serviks pada suatu Rumah Sakit Rujukan Tersier

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Abstract

Objective: To investigate the response of radiotherapy and related clinicopathologic characteristics on cervical cancer patients.

Methods: This was a retrospective study. Subjects were patients diagnosed with cervical cancer stage IIA-IIIB who had undergone radiation therapy based on standard protocol in our hospital, during the period of January 2014 to December 2015. The clinical factors of those patients, such as age, Body Mass Index, blood pressure, hemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter, the International Federation of Gynecology and Obstetrics (FIGO) staging, as well as pathologic characteristic, i.e histopathology and grading were recorded. During radiation protocol until 3 months post radiation, we also noted any side effects of gastrointestinal tract, genitourinary tract, and hematologic. Evaluation of radiotherapy response was based on Response Evaluation Criteria in Solid Tumors (RECIST).

Results: A total of 123 subjects were enrolled in this study. 84 cases or 68.29% was complete response, 30 cases or 24.39% was partial response, 6 cases or 4.88% was stable response, and 3 cases or 2.44% was progressive. Based on gastrointestinal side effect, there was no side effect or grade 0 on 99 cases (80.49%), grade 1 on 20 cases (16.26%), grade 2 on 4 cases (3.25%), grade 3 on 0 case (0%). Based on side effect of genitourinary, there was no side effect or grade 0 on 105 cases (85.37%), grade 1 on 17 cases (13.82%), grade 2 on 1 case (0.81%), grade 3 on 0 case (0%). Based on hematologic side effects, there was no side effect on 108 cases (87.80%), grade 1 on 15 cases (12.20%), grade 2 on 0 case (0%), grade 3 on 0 case (0%). Largest tumor diameter was statistically significant, with $p=0.036$ (RR 2.64 (1.07-6.56))

Conclusion: The majority of definitive-curative radiotherapy response on cervical cancer stage IIA-IIIB was complete (68.29%). Acute side effects involving the gastrointestinal, genitourinary, and hematologic system were commonly can be tolerable during and 3 months post radiation therapy. Clinicopathologic characteristics significantly associated with the complete response of radiotherapy was the largest tumor diameter.

[Indones J Obstet Gynecol 2017; 5-4: 230-235]

Keywords: largest tumor diameter, radiation response, radiation side effect

Abstrak

Tujuan: Respon terapi radiasi dan karakteristik klinis serta patologi yang berhubungan pada pasien kanker serviks di RSCM.

Metode: Penelitian kohort ini dilakukan dengan menggunakan data sekunder terhadap 123 pasien kanker serviks stadium IIA-IIIB yang menjalani radiasi kuratif definitif sesuai protokol standar bulan Januari 2014-Desember 2015 di RSUPN Dr. Cipto Mangunkusumo. Dilakukan pencatatan karakteristik klinis dan patologis sebelum radiasi. Dicatat juga efek samping akut gastrointestinal, traktus genitourinaria, dan hematologis selama menjalani protokol radiasi sampai 3 bulan pascaradiasi. Data respon tiga bulan pascaradiasi lengkap berdasarkan klinis dan pemeriksaan ultrasonografi trans-rektal/transvaginal dicatat dan diklasifikasikan sesuai Response Evaluation Criteria in Solid Tumors (RECIST).

Hasil: Dari 123 kasus, 84 kasus (68,29%) diperoleh respon komplit, 30 kasus (24,39%) respon parsial, 6 kasus (4,88%) respon stabil, dan 3 kasus (2,44%) respon progresif. Berdasarkan efek samping akut gastrointestinal, tidak didapatkan efek samping (derajat 0) pada 99 kasus (80,49%), derajat 1 pada 20 kasus (16,26%), derajat 2 pada 4 kasus (3,25%), derajat 3 pada 0 kasus (0%). Berdasarkan efek samping akut genitourinaria, tidak didapatkan efek samping (derajat 0) pada 105 kasus (85,37%), derajat 1 pada 17 kasus (13,82%), derajat 2 pada 1 kasus (0,81%), dan derajat 3 pada 0 kasus (0%). Berdasarkan efek samping akut hematologis, tidak didapatkan efek samping (derajat 0) pada 108 kasus (87,80%), derajat 1 pada 15 kasus (12,20%), derajat 2 pada 0 kasus (0%), dan derajat 3 pada 0 kasus (0%). Didapatkan hubungan bermakna antara diameter tumor ($p=0,036$; RR 2,64; IK95 1,07-6,56) dengan respon radiasi komplit.

Kesimpulan: Gambaran respon radiasi kuratif definitif pada kanker serviks stadium IIA-IIIB di RSCM adalah 68,29% respon komplit. Efek samping akut gastrointestinal, genitourinaria, dan hematologis pada umumnya tidak terjadi selama dan sampai 3 bulan pascaradiasi. Sebagian besar efek samping akut yang terjadi berderajat rendah. Terdapat hubungan bermakna antara diameter tumor terbesar dengan respon komplit radiasi. Tidak terdapat hubungan bermakna antara usia, Indeks Masa Tubuh, kadar hemoglobin, jumlah leukosit darah, kadar albumin serum, stadium FIGO, jenis histopatologis, dan derajat diferensiasi dengan respon terapi radiasi.

[Maj Obstet Ginekolog Indones 2017; 5-4: 230-235]

Kata kunci: diameter tumor terbesar, efek samping radiasi, respon radiasi

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INTRODUCTION

According to the World Health Organization (WHO), cervical cancer cases was the second number of all women cancer and the seventh number of all cancer around the world in 2010.¹ In Indonesia, cervical cancer is the second number of woman of age 15-44 years old. At Dr. Cipto Mangunkusumo hospital, cervical cancer number was 3112 cases found in 2007, which account for 75% of gynecologic cancer.² These magnitude of the incidence in Indonesia will add more health, economic, and social burden in this country, particularly for those women.

Another problem is the majority of them admitted on advanced stage, with relatively low survival rate. On advanced stage-IIb and higher, radiation can be used interchangeably with chemoradiation depend on patient condition. On their research, Iskandar, et al revealed that there was no difference in radiotherapy response among cervical cancer patients at Dr. Cipto Mangunkusumo hospital who underwent radiation only compare to chemoradiation.³ On the other side, few studies done previously in same hospital showed that it was difficult to a cervical cancer patient complete her chemoradiation course of treatment compare to radiotherapy.⁴ Therefore, radiation therapy could be a main modality for most of these patients. However, local tumor control of radiotherapy is still not satisfied yet, ranging from 20 to 50%. Failure to achieve local tumor control would increase the morbidity and the risk of developing distant metastasis. However, if successful, the survival rate could be increased as many as 50%.⁵

Factors influencing the radiotherapy response had been questioned and studied previously in numerous centers. If such factors were clearly identified and modified, it will gain our understanding in increasing radiotherapy response and hence survival. An acute side effect during the course could potentially making the patient not to continue the treatment. Therefore, we conducted a research to find out response rate of radiotherapy, incidence of acute side effect, and relation of routine and simple clinicopathologic characteristic-i.e age, Body Mass Index (BMI), blood pressure, blood hemoglobine level, blood leucocyte count, serum albumin level, tumor size, International Federation of Gynecology and

Obstetrics (FIGO) staging, histopathology and grading-of patients in our hospital.

METHODS

This retrospective study used secondary data from cervical cancer patients, who came to Dr. Cipto Mangunkusumo hospital, department of radiotherapy, during January 2014 to December 2015. The data of the subject was included for further analysis if the subject had been already diagnosed with cervical cancer based on histopathology examination, planned to have radiotherapy only based on standard protocol, i.e external curative dose of 46-50 Gy (25 times) using gamma ⁶⁰Co 1,2 megavolt and LINAC 4-10 Mega Volt continued to brachytherapy using after loading method HDR microselectron unit of ¹²⁵I, dose 700cGy, three times on A-point. Subjects suffering other primary tumor as well as incomplete data were excluded.

The clinical factors of those patients prior to radiation, such as age, Body Mass Index, blood pressure, hemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter FIGO staging and pathologic characteristic, i.e histopathology and grading were recorded. During radiation protocol until 3 months post radiation, we also noted any side effects of gastrointestinal tract, genitourinary tract, and hematologic. Evaluation of radiotherapy response was based on Response Evaluation Criteria in Solid Tumors (RECIST). The collected data was further analysed using Stata 13.

RESULTS

We had 123 cases for further analysis. The baseline characteristic is shown in table 1. Among 123 cases, 84 cases or 68.29% was complete response, 30 cases or 24.39% was partial response, 6 cases or 4.88% was stabile response, and 3 cases or 2.44% was progressive. Based on gastrointestinal side effect, there was no side effect or grade 0 on 99 cases (80.49%), grade 1 on 20 cases (16.26%), grade 2 on 4 cases (3.25%), grade 3 on 0 case (0%) Based on side effect of genitourinary, there was no side effect or grade 0 on 105 cases (85.37%), grade 1 on 17 cases (13.82%), grade 2 on 1 case (0.81%), grade 3 on 0 case (0%). Based on hematologic side effects, there was no side effect on 108 cases (87.80%), grade 1 on 15 cases (12.20%), grade 2 on 0 case (0%), grade 3 on 0 case (0%).

On bivariate analysis, p of each factors were age ($p=0.266$; RR 0.87 (0.67-1.12)), Body Mass Index ($p=0.397$), blood pressure classification ($p=0.658$; RR 0.98 (0.76-1.27)), largest tumor diameter ($p=0.034$; RR 1.30 (1.03-1.63)), hemoglobin level ($p=0.193$; RR 0.98 (0.76-1.27)), blood leucocyte count ($p=0.969$; RR 1.00 (0.78-1.29)), FIGO staging

(II vs III) ($p=0.526$; RR 1.08 (0.85-1.38)), histopathology result (squamous cell carcinoma vs nonsquamous cell carcinoma) ($p=0.159$; RR 1.18 (0.90-1.55)), and grading ($p=0.469$) (Table 2). On multivariate analysis, tumor diameter was statistically significant, with $p=0.036$ (RR 2.64 (1.07-6.56)) (Table 3).

Table 1. Characteristics of Cervical Cancer Patients Underwent Radiation treatment only during January 2014 - December 2015

Characteristics	n (%)	Mean $\pm$ SD	Median (min-max)
Clinical Characteristics Age (years):		50 $\pm$ 9	51 (26-74)
26-49	51 (41.46)		
50-74	72 (58.54)		
Body Mass Index (BMI) (kg/m²):		23.98 $\pm$ 4.77	23.7 (14.3-46.6)
< 18.5	10 (8.13)		
18.5 - 22.9	46 (37.40)		
$\geq$ 23	67 (54.47)		
Blood pressure (mmHg):		130.17 $\pm$ 19.50 / 79.68 $\pm$ 11.43	129 (90-189) / 82 (54-114)
Hypertension	43 (34.96)		
No Hypertension	80 (65.04)		
Blood hemoglobin level (g/dl)		11.48 $\pm$ 1.45	11.3 (7.3-15.8)
< 10	12 (9.76)		
$\geq$ 10	111 (90.24)		
Blood leucocyte count (cell/mm³)		9589 $\pm$ 4082	8480 (2960-19410)
$\leq$ 10.000	76 (61.79)		
> 10.000	47 (38.21)		
Serum albumin level (g/dl) :		3.99 $\pm$ 0.73	4.2 (1.27-4.89)
< 3.5	9 (19.15)		
$\geq$ 3.5	38 (80.85)		
Largest tumor diameter (mm)		45.79 $\pm$ 18.78	40 (15-102)
< 40	45 (36.59)		
$\geq$ 40	78 (63.41)		
FIGO Staging		N/A	N/A
Stage IIA	4 (3.25)		
Stage IIB	42 (34.15%)		
Stage IIIA	7 (5.69)		
Stage IIIB	70 (56.91)		
PATHOLOGY CHARACTERISTICS			
Histopathology type		N/A	N/A
Squamous cell carcinoma	89 (72.36)		
Adenosquamous carcinoma	9 (7.32)		
Adenocarcinoma	24 (19.51)		
Neuroendocrine	1 (0.81)		
Differentiation (grading)		N/A	N/A
Good	44 (35.77)		
Moderate	58 (47.15)		
Poor	21 (17.07)		

Table 2. Bivariate Analysis

Characteristic		Complete Response		No Complete Response		p	RR	CI 95%
		n	%	n	%			
Age (years)	26-49	32	38.10	19	48.71	0.266	0.87	0.67-1.12
	50-7	52	61.90	20	51.29			
Blood pressure	Hypertension	29	34.52	14	35.90	0.882	0.98	0.76-1.27
	Non Hypertension	55	65.48	25	64.10			
Blood hemoglobin level	< 10	6	7.14	6	15.38	0.193*	0.71	0.40-1.27
	≥ 10	78	92.86	33	84.62			
Body Mass Index (BMI)	Overweight	48	55.81	19	51.35	0.397	1.06	0.83-1.34
	Non overweight	38	44.19	18	48.65			
Blood Leucocyte Count (cells/ μ l)	≤ 10.000	52	61.90	24	61.54	0.969	1.00	0.78-1.29
	> 10.000	32	38.10	15	38.46			
FIGO stage	Stage II	33	39.29	13	33.33	0.526	1.08	0.85-1.38
	Stage III	51	60.71	26	66.67			
Largest tumor diameter (mm)	< 40	36	42.86	9	23.08	0.034	1.30	1.03-1.63
	≥ 40	48	57.14	30	76.92			
Histopathology type	Squamous Cell Carcinoma	65	75.58	24	64.86	0.159	1.18	0.90-1.55
	Non Squamous Cell Carcinoma	21	24.42	13	35.14			
Differentiation	Good	33	39.29	11	28.21	0.469	N/A	N/A
	Moderate	38	45.24	20	51.28			
	Poor	13	15.48	8	20.51			
Serum Albumin Level	< 3.5	5	14.71	4	30.77	0.198*	0.73	0.44-1.20
	≥ 3.5	29	85.29	9	69.23			

*Fisher's exact test

Table 3. Multivariate Analysis

Variable	Coef.	OR	SE	p	IK95%	
					Min	Max
Hemoglobin	-0.756	0.47	0.30	0.230	0.14	1.61
Tumor diameter	0.973	2.64	1.23	0.036	1.07	6.56
Histopathology type	-0.549	1.73	0.76	0.213	0.73	4.11
Constant	-0.997					

DISCUSSION

The majority of the subjects had complete response, i.e 84 cases or 68.29%. This result showed that our radiotherapy response is relatively good, even though it is lower than previous study-i.e 81.6% - on 38 patients in 2009 reported by radiotherapy division of Dr. Cipto Mangunkusumo Hospital.⁶ The difference could be linked

to sample size and length of observation time. However, study by Amin, et al in Dr. Soetomo Hospital, Surabaya found similar result, i.e 70.4% and no complete response 29.6%.⁷ Whether this rate could be generalize as successful rate of radiotherapy response of cervical cancer patients in Indonesia should be further elaborated and analized, considering that the protocol and subject characteristics are still vary among centers.

This study also revealed that most of our subject had low grade acute side effect, most experience no side effect. All patient could complete the course of treatment regardless this side effect. It further stated that compare to chemoradiation with the same effectivity, the side effect of radiation is much tolerable.

Age has been shown as a clinical prognostic factor for local control and survival in some studies. Elantholi, et al revealed that age > 50 yo was linked with higher no residual tumor.⁸ In our study, more younger patient was found, but we still can not prove its direct relationship with lower complete response. Clinically, age group 26-50 yo tend to decrease response 0.87 times compare to age group > 50 yo. But statistically, age is not significant determinant for complete response.

Simple nutritional status measured by BMI showed that most of our subjects was overweight to obese. This finding against the perception that cancer patients on advanced stage was always malnourished. Furthermore, the higher BMI on advanced staged patients will add more risk of mortality due to non cancer related factors.⁹ This study showed that there is no significant relation between BMI and complete response. Albumin level as another way for measurement showed that most of our subjects was not in hypoalbuminemic state. Clinically said, albumin level < 3.5 g/dl tend to decrease response 0.73 times, but remain statistically insignificant.

Previous studies showed that cancer lesion diameter > 4 cm will be hard for being treated compare to smaller size due to high association with early onset distant metastasis.¹⁰ Additionally, larger tumor size often linked with radioresistant cells due to high rate of mutation.¹¹ Eiffel et al studied 1526 patients underwent radiation only found that control rate was 97% on tumor diameter < 5 cm and 84% on tumor diameter 5-7 cm.¹² Our finding showed that tumor size < 40 mm was linked with better complete response (2.64 times) compare to tumor size $\geq$ 40 mm with statistically significant result on both bivariate and multivariate analysis.

More than half of subjects in our study was in the stage IIIB. It showed that there was still many patients came in late stage which was potentially making the treatment become difficult. This condition was different to India, as in Chufal et al's study showed that most of their patients was in

stage IIB.¹² Regardless the fewer earlier stage in our subject, we still had 4 cases of stage IIA who underwent radiation therapy eventhough it was not our standard procedure to include them in radiation treatment. Due to patient preference to refuse surgery, 3 patients asked for radiation treatment. One patient had undergone laparotomy but found inoperable and further continued to radiotherapy. On bivariate analysis, we did not find significant association of FIGO stage with radiotherapy response.

Squamous cell carcinoma remains the most common type as in our study, followed by adenocarcinoma. Garcia-Arias, et al in their study also have similar finding. Recently there was increasing incidence of adenocarcinoma but decreasing incidence of squamous cell carcinoma. It could be linked to better diagnostic classification used, obesity, and more younger age at diagnosis.¹³ Reagen and Wentz stated that adenocarcinoma was less sensitive to radiation that lead to poor survival of such type. Meanwhile Fletcher, et al also believed that poor survival of such type was linked to miometrial invasion, thus it could spare the radiation in most of treatment.¹⁴ However, in our study, the response of radiotherapy of squamous cell carcinoma group was comparable to non squamous cell carcinoma.

Cervical cancer prognosis is also linked to differentiation or grading. In our study, more subjects was good and moderate differentiation, similar with findings by Chufal, et al.¹² On the other side, the difference in grading will not result in diferrence in radiotherapy response.

CONCLUSION

Most of definitive-curative radiotherapy responses on cervical cancer stage IIA-IIIB were complete (68.29%). Partial response was 24.49%, stable response was 4.88%, and progressive was 2.44%. The Acute side effects involving the gastrointestinal, genitourinary, and hematologic system could be tolerated during and 3 months post radiation therapy. The clinical characteristic that significantly related to complete response of radiotherapy was largest tumor diameter.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence

- and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 11/ July/2016.
2. Azis MF. Masalah Kanker Serviks. *Cermin Dunia Kedokteran* 2001; 133: 5-7.
 3. Iskandar, Andrijono, Supriana. Uji Klinik Kemoradiasi dibanding radiasi terhadap respon infeksi HPV dan respon klinik pada karsinoma sel skuamosa uteri. *Maj Obstet Ginekol Indones* 2008; 32(4): 212-22.
 4. Nuranna L, Gunawan R, Supriana N, Sutrisna B. Efek Toksisitas dan Respon Terapi Radiasi dibanding Kemoradiasi pada Kanker Serviks Stadium Lanjut Lokoregional di RSUPN Dr. Cipto Mangunkusumo. Program Pendidikan Konsultan Onkologi Ginekologi FKUI-RSCM: 2011.
 5. Jacobs AJ, Faris C, Perez C, Kao M, Galakatos A, Camel M. Short-Term Persistence of Carcinoma of The Uterine Cervix After Radiation, An Indicator of Long Term Prognosis. *Cancer* 1986; 57: 944-50.
 6. Supriana N. Uterine Cervix Cancer Patient FIGO IIB - IVA, January 2009 - December 2009, Radiotherapy Department, Dr. Cipto Mangunkusumo Hospital. 2009.
 7. Amin Y, Mulawardhana P, Erawati D. Demografi, Respon terapi dan Survival Rate Pasien Kanker Serviks Stadium III-IVA yang mendapat Kemoterapi Dilanjutkan Radioterapi. *Maj Obstet Ginekol*, 2015; 23(3): 97-105.
 8. Elantholi, Sushmita Ghoshal, Vinay Kumar, Rakesh Kapoor. Prognostic value of response to external radiation in stage IIB cancer cervix in predicting clinical outcomes: A retrospective analysis of 556 patients from India. *Radiotherapy Oncol*, 2006; 79: 142-6.
 9. Kizer NT, Thaker PH, Gao F, Zigelboim I, Powell MA, Rader JS, Mutch DG, Grigsby PW. The Effects of Body Mass Index on Complications and Survival Outcomes in Patients With Cervical Carcinoma Undergoing Curative Chemoradiation Therapy. *Cancer* 2011; 117: 948-56.
 10. Yaes RJ. Tumor heterogeneity, tumor size and radio resistance. *Int J Radiat Oncol Biol Phys*. 1989; 17: 993-1005.
 11. Wang, Wang, Yang, Chai, Shi, Lkiu. Patient age, tumor appearance and tumor size are risk factors for early recurrence of Cervical Cancer. *Mol Clin Oncol*, 2015; 3: 363-6.
 12. Chufal KS, Chufal, Madhup Rastogi, Srivastava M, Pant MC, Bhat MLB, Srivastava K. Concurrent chemoradiotherapy for locally advanced cervical cancer using Gemcitabine: non-randomized comparison of three sequential protocols. *Cancer Therapy* 2007; 5: 43-54.
 13. Garcia-Arias, Candelaria, Cetina, et al. The prognostic significance of leukocytosis in cervical cancer. *Int J Gynecol Cancer* 2007; 17: 465-70.
 14. Fletcher GH. *Am. J. Roentgenol. Rad. Ther. Nucl. Med.* 1971; 111: 225.

Research Article

The Risk of Ovarian Malignancy Algorithm (ROMA) as a Predictor of Ovarian Tumor Malignancy

Risk of Ovarian Malignancy Algorithm (ROMA) sebagai Prediktor Keganasan Ovarium

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Abstract

Objective: To assess the diagnostic value of Risk of Ovarian Malignancy Algorithm (ROMA) in predicting ovarian malignancy.

Methods: Diagnostic test was performed at dr. Mohammad Hoesin Hospital Palembang during June 2016 to November 2016. Data were analyzed with SPSS version 21.0 and Med-calc statistic.

Results: A total of 57 subjects were recruited in this study. Subjects were divided into two groups: the premenopausal and postmenopausal group. Analysis with ROC curve was performed, the ROMA optimal cut-off of ROMA was 23.7% and 48.15% in the premenopausal and the post-menopausal group, respectively. With the optimal cut-off, the sensitivity was 79.41% and specificity was 75%, positive predictive value was 73.07% and negative predictive value 83.77% with accuracy 76.92% in diagnosing ovarian malignancy. Compared to RMI-3, the sensitivity was 65.5% and specificity was 85.7% with accuracy 75.44%.

Conclusion: ROMA is not a reliable diagnostic tools of ovarian malignancy.

[Indones J Obstet Gynecol 2017; 5-4: 236-240]

Keywords: CA125, HE4, ovarian cancer, risk of ovarian malignancy algorithm/ROMA, risk of ovarian malignancy index/RMI

Abstrak

Tujuan: Menilai nilai diagnostik Risk of Ovarian Malignancy Algorithm (ROMA) dalam memprediksi keganasan ovarium.

Metode: Penelitian uji diagnostik dilakukan di RSUP dr. Mohammad Hoesin Palembang selama periode Juni 2016 - November 2016, sebanyak 61 wanita dengan tumor ovarium dimasukkan sebagai subjek penelitian, 4 pasien dieksklusi karena perbedaan diagnosis saat intraoperatif. Data kemudian dianalisis dengan menggunakan software SPSS versi 21.0 dan Med-calc statistic.

Hasil: Dari 57 pasien yang memenuhi kriteria inklusi dan eksklusi. Pasien dibagi menjadi dua kelompok yaitu kelompok premenopause dan menopause. Dilakukan analisis dengan kurva ROC didapatkan cut-off optimal ROMA pada penelitian ini yaitu 23,7% untuk kelompok premenopause dan 48,15% untuk kelompok menopause. Dilakukan uji diagnostik, didapatkan sensitivitas 79,41% dan spesifisitas 75%, nilai duga positif adalah 73,07% dan nilai duga negatif 83,77% dengan nilai akurasi 76,92% dalam mendiagnosa keganasan ovarium. Dibandingkan dengan RMI-3, didapatkan nilai sensitivitas 65,5% dan spesifisitas 85,7% dengan nilai akurasi 75,44%.

Kesimpulan: Pemeriksaan ROMA bukan merupakan uji diagnostik keganasan ovarium yang akurat.

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Kata kunci: CA-125, HE-4, kanker ovarium, risk of ovarian malignancy algorithm, risk of ovarian malignancy index

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INTRODUCTION

Ovarian cancer is the sixth most common malignancy in women after uterine cervical, breast, colorectal, skin, and lymphoma cancer. Up to 70% of ovarian cancer is diagnosed at advanced stage that have spread into upper abdominal cavity (stage III) or wider (stage IV) with 5 years survival rate at 15-20%, whereas survival rate at stage I and stage II are predicted at lower rate of 90% and 70%.^{1,2}

Patients are mostly diagnosed at more advanced stage as early diagnostic tool is still not available. One of the mostly used tumor markers is cancer antigen (CA) 125. To date, CA 125 is the best tumor marker available in diagnosing and monitoring ovarian cancer patients. However, CA 125 increases only in 80% of patients in late stages and 50% of patients in early stages. About 20% of patients of early stages ovarian cancer have normal CA 125 values.²

Several biomarkers have been tested lately as alternatives or additional markers to differentiate benign from malignant tumor. Human Epididymis4 (HE4) is a promising biomarker to be used. HE4, a glycoprotein, is over expressed in ovarian cancer particularly.³

Moore et al. designed Risk of Ovarian Malignancy Algorithm (ROMA), using blood test algorithm, as a simpler biomarker compared to RMI (risk malignancy index) that requires ultrasonography. They reported significant increase in sensitivity and specificity when HE4 and CA125 are used in combination. In a further study comparing ROMA and RMI, Moore et al. reported higher sensitivity and specificity in ROMA.^{4,5}

Karlsen et al. reported a high sensitivity (94.8%) and specificity (75%) results of ROMA in diagnosing ovarian cancer.⁶ Molina et al. also reported a better sensitivity (90.1%) and specificity (87.1%) results of ROMA compare to CA125, but it is might further improved if it is used with normal HE4 and abnormal CA125.⁷

RMI is one of the most frequent used methods in identifying malignancy and considered as a simple method which uses menopause status, ultrasound and CA125 level. Jacobs et al. obtained sensitivity of 85.4% and specificity of 96.9% using cut-off 200. However, Andriata et al. obtained a different results in using the same RMI method: sensitivity of 8.4% and specificity of 76.9%.⁸

Anton et al. from Brazil did the same comparison of ROMA and RMI and no significant difference was found between diagnostic values of ROMA and RMI.⁹ Normal value of biomarkers such as CA125 and HE4 varies in different population. Pauler et al. reported a difference in normal value of CA125 in Caucasian and Asian. Several studies have been done to find normal values of these markers in different populations. This difference in normal values could alter the outcome of ROMA. Therefore, Karen et al. proposed different cut-off values for different population to accommodate this variation of normal values in different population.¹⁰ This study is aimed to assess the diagnostic value of ROMA in predicting ovarian malignancy.

METHODS

Diagnostic tests and cross sectional design were used on 61 women with ovarian cancer and were

planned for operative procedure. This research was conducted at Obstetrics and Gynecologic Department of Dr. Mohammad Hoesin Palembang Hospital from June 2016 to November 2016.

Inclusion criteria were women diagnosed with ovarian cancer who are being planned to undergo surgical procedures. The diagnosis of ovarian cancer was based on anamnesis, physical examination, and ultrasonography. Exclusion criteria were women diagnosed with non-gynecologic malignancies, pregnancy, kidney failure or intra-operative mass of non-ovarian origin.

Gestational age, parity, education level, occupation, smoking, contraception, physical examination, ultrasonography, post-operative CA125 and HE4 of the subjects were recorded. CA125 and HE4 tests were carried out by using architect reagent and histopathology results were masked. ROMA score was calculated by software downloaded from <http://romatools.he4test.com/>.

Data were analyzed with SPSS 21.0. The cut-off point value of ROMA was determined by Receiving Operating Characteristic (ROC) curve. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio were calculated by med-calc statistic.

RESULTS

Demographic and the tumor characteristics of the subjects are presented in Table 1. Mean age of samples was 40.51 years old with majority of the patients were from pre-menopause group (56.1%) and higher tendency found in multipara (43.9%).

Table 1. Demographic and Tumor Characteristics of the Subjects

Characteristic	Frequency	
	N	%
Age, mean±SD	40.51±16.32 (6-64)	
Pre-menopause	32	56.1
Menopause	25	43.9
Parity		
Not Married	11	19.3
Primipara	21	36.8
Multipara	25	43.9
Pathology		
Malignant	24	42.2
Borderline	5	8.7
Benign	28	49

Type		
Epithelial	45	78.9
Non-Epithelial	12	21.1
Total	57	100

In this study, alternative cut-off point of ROMA was determined by using ROC curve. Patients were divided into two groups, consisting of the pre-menopausal and post-menopausal group. For the post-menopausal the group, the optimal cut-off point of ROMA was obtained at 58.15% with sensitivity of 47.15%, specificity of 71.4%, positive predictive value of 86.6% and negative predictive value of 50% as shown in Figure 1 below.

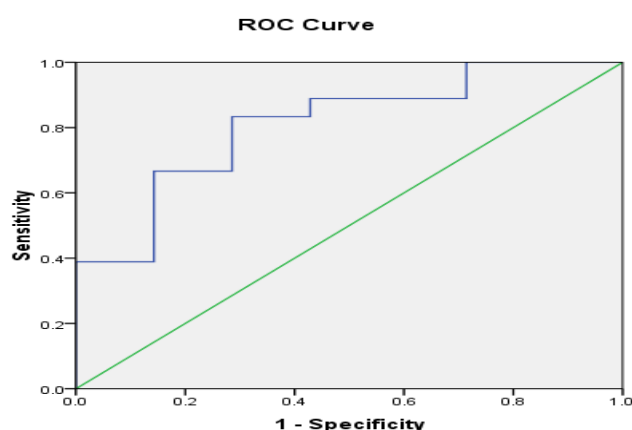


Figure 1. ROC curve of ROMA of the post-menopausal group

In the pre-menopausal group, the optimal cut-off point of ROMA was obtained at 23.7% with sensitivity of 72.72% and specificity of 76.19%, positive predictive value of 61.54% and negative predictive value of 84.21% (Figure 2).

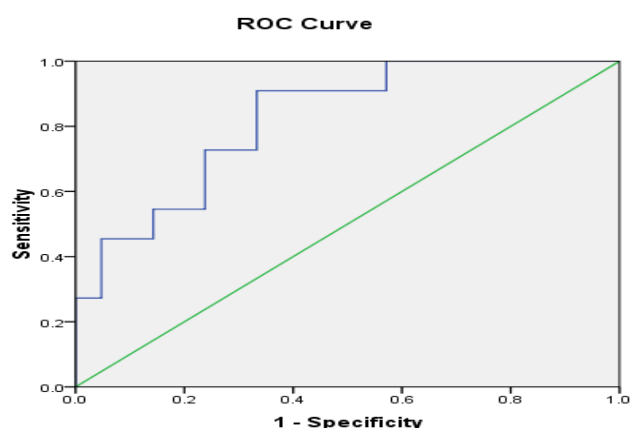


Figure 2. ROC curve of ROMA of the pre-menopausal group

Diagnostic test was done with alternative cut-off with borderline histopathology was included as malignant group. Results obtained were then compared to those of standard cut-off. As RMI-3 is frequently used to predict malignant to benign ovarian tumor, we also compared ROMA to RMI-3 with standard cut-off > 200 for prediction of malignancy (Table 2).

Table 2. Diagnostic Value of RMI-3 vs ROMA Alternative vs ROMA Standard with Borderline Included

Benign vs Malignant + Borderline	ROMA alternative	ROMA standard	RMI-3
Sensitivity, %	65.5	82.7	65.5
Specificity, %	85.7	64.2	85.7
PPV, %	82.6	70.5	82.6
NPV, %	70.5	78.2	70.5
Accuracy, %	75.44	73.68	75.44

If samples with borderline histopathology were not included as malignant group, better diagnostic results were obtained. RMI-3 have better sensitivity and specificity compared to ROMA results without borderline histopathology included as shown in Table 3.

Table 3. Diagnostic Value of RMI-3 vs ROMA Alternative vs ROMA Standard with Borderline Excluded

Benign vs Malignant	ROMA alternative	ROMA standard	RMI-3
Sensitivity, %	79.41	91.67	70.83
Specificity, %	75	64.2	85.7
PPV, %	73.07	68.75	90.47
NPV, %	83.77	90.00	77.41
Accuracy, %	76.92	76.92	78.84

DISCUSSION

Almost 70% of ovarian cancer were diagnosed at later stage with 5-year survival rate at about 15-20%, whereas survival rate at stage I and stage II were predicted at 90% and 70%.

ROMA, a test using combination of CA125, HE4, and menopause status, is an effective diagnostic tool to diagnose ovarian cancer. The effectiveness of ROMA as pre-operative diagnosis tool in patients with pelvic mass have been proven by several

studies though there are still doubts of its superiority due to variations in cut-off values to diagnose malignancy.

Gorp et al. and Anton et al. have shown different cut-off values for different populations resulting in different diagnostic values. Hence, this study is aimed to find an alternative cut-off value to be compared with standard cut-off value and RMI which often used as a diagnostic tool.^{7,8,11,12}

In this research, by using ROC analysis, alternative cut-off values were obtained at 23.7% for pre-menopause and 48.15% for menopause (72.41% sensitivity, 75% specificity, 73.68% accuracy) when patients with borderline histopathology were included as malignant group. Better results were obtained (79.41% sensitivity, 75% specificity, 76.68% accuracy) when patients with borderline histopathology were not included in malignant group. Using standard cut-off, ROMA has better sensitivity (82.7% including borderline; 91.67% if borderline was excluded).

RMI-3 diagnostic value was also improved when borderline histopathology was not included in the malignant group: 70.83% for sensitivity; 85.7% for specificity; and 78.84% for accuracy.

In this study, the median age was 40.51 years old which is close to Winarto's median age of 41 years old, and the proportion of the post-menopausal women was 37.8%. There were also differences in the dominant type of tumor. Mucinous type of ovarian carcinoma was more dominant (41%) in this research compared to Moore's, Molina's and Karlsen's in which serous type of ovarian cancer was more dominant (>75%).^{4,5,9,10}

Sensitivity and specificity of ROMA in this study are lower compared to Moore's, Van Gorp's and Chudezka's. These differences may be attributed to different demographic data in which past menopausal patients were more dominant in Moore's (53.3%), Van Gorp's (53.2%) and Chudezka (61.9%) while in this study pre-menopausal group was dominant (56.1%).^{4,11,12} In this study, when diagnostic test was done for post-menopausal group, ROMA with standard cut-off gives better sensitivity and accuracy (88.9% and 80%). This result showed that ROMA probably gave a better performance when used in the menopausal group.

RMI method was first designed by Jacobs et al. by using ultrasonography combined with CA₁₂₅ value. In this study, no difference was found between RMI and ROMA. However, the accuracy of RMI3 was the highest, which is amounted to 78.85% in subjects with borderline histopathology not included as malignancy.

The limitations of this study were smaller samples compared to previous studies and no FSH measurement done to differentiate post-menopausal and pre-menopausal subjects.

CONCLUSION

ROMA is not a reliable diagnostic tool. Compared to RMI3, ROMA has lower sensitivity. Overall, RMI3 has a better diagnostic value compare to ROMA.

REFERENCES

1. Aziz MF. Gynecological cancer in Indonesia. *J Gynecol Oncol.* 2009; 20: 1: 8-10.
2. Tavasolli FA. Tumours of the ovary and peritoneum. in: Devilee P. WHO Classification of tumours pathology and genetics tumours of the breast and female genital organs. Lyon: IARC Press.; 2003: 114-92.
3. Hellstrom I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, et al. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. *Cancer Res.* 2003; 63: 3695-700.
4. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol.* 2008; 108: 402-8.
5. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing HE4 and CA₁₂₅ for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol Oncol.* 2009; 112: 40-6.
6. Karlsen MA, Sandhu N, Høgdal C, Christensen, et al. Evaluation of HE4, CA₁₂₅, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. *Gynecol Oncol.* 2012; 127: 379-83.
7. Andriahta Z, Saleh AZ, Sastradinata I. Akurasi Uji Diagnostik Risk of Malignancy Index dan Indeks Novel dalam Memprediksi Keganasan Ovarium. Thesis Departemen Obstetri dan Ginekologi RSMH. 2013: p39-58
8. Anton C, Carvalho FM, Oliveira EI, Maciel GAR, Baracat EC, Carvalho JP. A comparison of CA₁₂₅, HE4, risk of ovarian malignancy algorithm (ROMA) and the risk of malignancy index (RMI) for the classification of ovarian masses. *Clin.* 2012; 67: 437-41.
9. Molina R, Escudero JM, Auge JM, Filella X, Foj L, Torne A, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA₁₂₅ and ROMA algorithm in patients with gynecological diseases. *Tumor Biol.* 2011; 32: 1087-95.

10. Winarto H, Laihad JB, Nuranna L. Modification of cut off values for HE₄, CA₁₂₅, the risk of ovarian malignancy index and the risk of malignancy algorithm for ovarian cancer detection in Jakarta Indonesia. *Asian Pac J Cancer Prev*. 2014; 15: 1949-53.
11. Van Gorp T, Cadron I, Despierre E, Daemen A, Leunen K, Amant F et al. HE₄ and CA₁₂₅ as a diagnostic test in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. *Br J Cancer*. 2011; 1; 104(5): 863-70.
12. Chudezka A, Ploska AC, Menkiszak J, Rzechula AS, Stjona A, Byra E, et al. Preoperative diagnostic performance of ROMA (risk of ovarian malignancy algorithm) in relation to etiopathogenesis of epithelial ovarian tumor. *J Mol Biomark Diagnos*. 2013: S4-003.

Research Article

The Accuration of Liquid-Based Cytology and HPV DNA Test Combination as Precervical Cancer Lesion Screening

Akurasi Pemeriksaan Kombinasi Liquid-Based Cytology dan Tes DNA HPV sebagai Penapis Lesi Prakanker Serviks

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Abstract

Objective: To investigate the accuracy of liquid-based cytology, HPV DNA test, and the combination of liquid-based cytology and HPV DNA test, compared to histopathology as the gold standard of precervical cancer lesion screening.

Methods: This was a cross-sectional study. The medical records of patients who came to the Women's Health Clinic of Dr. Cipto Mangunkusumo Hospital during the period of July 2013 to December 2015 were evaluated.

Results: The high risk type HPV DNA is detected in 76% CIN 1, 88.46% CIN 2, and 84.21% CIN 3 in histopathology results. The accuracy of liquid-based cytology; sensitivity 88.54%, specificity 35.71%, PPV 75.89%, and NPV 57.69%. The accuracy of HPV DNA; sensitivity 81.25%, specificity 78.57%, PPV 89.66%, and NPV 64.71%. The accuracy of combination: sensitivity 94.79%, specificity 35.71%, PPV 77.12%, and NPV 75%.

Conclusion: The addition of HPV DNA test increased the sensitivity from 88.54% to 94.79% because of decreasing of false negative of liquid-based cytology. This thing has showed that the combination of liquid-based cytology and HPV DNA test could be one of the option of precervical cancer lesion screening method, especially in secondary or tertiary health center in Indonesia.

[Indones J Obstet Gynecol 2017; 5-4: 241-245]

Keywords: accuracy test, HPV DNA, liquid-based cytology, precervical cancer lesion, precervical cancer lesion screening

Abstrak

Tujuan: Diketuainya angka akurasi liquid-based cytology, DNA HPV, dan kombinasi keduanya dibandingkan dengan hasil histopatologi.

Metode: Penelitian ini merupakan penelitian potong lintang dengan jumlah sampel 138 subjek pada Juli 2013 - Desember 2015 di RS Dr. Cipto Mangunkusumo Kencana.

Hasil: DNA HPV tipe risiko tinggi terdapat pada 76% NIS 1, 88,46% NIS 2, dan 84,21% NIS 3 pada hasil histopatologi. Didapatkan akurasi pemeriksaan liquid-based cytology; sensitivitas 88,54%, spesifisitas 35,71%, NPP 75,89%, dan NPN 57,69%. Akurasi pemeriksaan DNA HPV; sensitivitas 81,25%, spesifisitas 78,57%, NPP 89,66%, dan NPN 64,71%. Sementara akurasi kombinasi keduanya adalah sensitivitas 94,79%, spesifisitas 35,71%, NPP 77,12%, dan NPN 75%.

Kesimpulan: Penambahan pemeriksaan DNA HPV meningkatkan angka sensitivitas dari 88,54% menjadi 94,79% karena turunnya angka negatif palsu pemeriksaan LBC. Hal ini menjadikan kombinasi pemeriksaan liquid-based cytology dan DNA HPV dapat menjadi pilihan metode penapisan lesi pra-kanker serviks terutama pada fasilitas kesehatan sekunder ataupun tersier di Indonesia.

[Maj Obstet Ginekol Indones 2017; 5-4: 241-245]

Kata kunci: DNA HPV, lesi prakanker serviks, liquid-based cytology, penapisan lesi prakanker serviks, uji akurasi

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INTRODUCTION

Cervical cancer is the third most female malignancy in the world and the second most in Indonesia; The Globocan Project in 2012 stated that the incidence of cervical cancer was 20928 cases and mortality rate was 9498 cases annually.^{1,2} Data from several hospitals in Jakarta reported the 5-year survival rate of cervical cancer stage I, II, III, and IV were 50%, 40%, 20%, and 0% respectively.³ Both the incidence and mortality rate of cervical cancer were well-correlated with cervical cancer

prevention program; particularly the precervical cancer lesion triage program such as visual inspection of acetic acid, cytology-based screening, colposcopy, and optoelectric.⁴ The high incidence of cervical cancer in several developing countries, especially in Indonesia, was the result of inadequacy of screening programs in detecting the cervical cancer in its initial process, precervical cancer lesion. On the contrary, cytology-based screening have already been well established and organized to be a routine screening program of

precervical cancer lesion screening program in some developed countries. Cytology-based screening has already been modified to liquid-based cytology in which aimed to lower the unsatisfactory result and improve the sensitivity.⁷ Previous studies showed that the sensitivity of liquid-based cytology varied from 76.2% to 96.24%.^{5,6}

The HPV DNA test has a high sensitivity as a precervical cancer screening tool, especially in the above 30-year old female population, there of in several developed countries the HPV DNA test is used as a triage screening tools.^{7,8} Some studies reported that HPV DNA test sensitivity was ranged 94.7% to 97.4%.^{7,9} The additional HPV DNA test was alleged to be the co-testing which could be combined to the cytology screening in order to increase the sensitivity of precervical cancer screening program on account of its high sensitivity. The co-testing of liquid-based cytology and HPV DNA test intended to increase the sensitivity and lower the false negative rate in cytology-based screening tool. Furthermore, not with standing the high cost of both liquid-based cytology and HPV DNA test, this co-testing was allegedly reported to increase the sensitivity which crucial and important parameter for screening tool. To date, there were no data and report corresponded to this co-testing of liquid-based cytology and HPV DNA test in Indonesia. This study is expected to be the reference for some options in precervical cancer screening tool, especially in secondary or tertiary health care center.

METHODS

This cross-sectional study was carried out at the Women's Health Center Dr. Cipto Mangunkusumo Hospital, Jakarta from July 2013 to December 2015. We collected data from medical records of patients who went to the Women's Health clinic of Dr. Cipto Mangunkusumo Hospital from other health center referral or those who came by her own will to have a precervical cancer lesion screening program. The inclusion criteria were 20 - 65 years old and those who were sexually active. These patients were offered the co-testing of liquid-based cytology and HPV DNA test, which continued with colposcopy. If the result of colposcopy was normal, they would not undergo biopsy (LEEP or LLETZ); meanwhile those with abnormal colposcopy results would undergo

biopsy (LEEP or LLETZ). The cervical cancer result of histopathology was excluded in this study.

The data were run into sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) analysis for each examination consisting of liquid-based cytology, HPV DNA test, and histopathology. This analysis was performed through SPSS24.0 for Windows®.

RESULTS

There were 138 subjects recruiting to this study. All of subjects were ranged from 22 - 65 years old with mean age was 41.96 years old. Of these 138 subjects, 55 patients (39.9%) were parity of 3.

Table 1 pointed out that the results of liquid-based cytology of LSIL is at the most proportion sample with 33.3% and ASCH is the least proportion in this study with 3.6%. Aside from that, high-risk type HPV DNA was detected in 63% samples where it consisted of single DNA was detected in 34.1%, combination of high risk and low risk type with 1.4%, and the combination of high risk type with 27.5%; in which these high risk type HPV DNA, type 16 was the most proportion with 28.1%, followed by type 18 and type 52 (23.97% and 17.36 respectively).

Table 1. Characteristic of Liquid-Based Cytology, HPV DNA Test, and Histopathology Result

Examination	N (%)
Liquid-Based Cytology	
Negative	26 (18.8)
ASCUS	29 (21)
LSIL	46 (33.3)
HSIL	32 (23.2)
ASCH	5 (3.6)
HPV DNA Test	
Negative / Not Detected	44 (31.9)
Low Risk Type	7 (5.1)
High Risk Type	
Single	47 (34.1)
Combination of High Risk - Low risk	2 (1.4)
Combination of High Risk	38 (27.5)
Histopathology	
CIN1	50 (36.2)
CIN2	26 (18.8)

CIN3	19 (13.8)
Non CIN	43 (31.2)
Total	138 (100)

Of 50 samples of CIN 1, high risk HPV DNA was detected in 38 samples (76%); meanwhile of 26 samples of CIN 2, high risk HPV DNA was positive in 88.46%; and of 19 samples of CIN 3, there was 84.21% high risk HPV DNA (Table 2). Furthermore, high risk HPV DNA were detected in 62.07% of ASCUS, 67.4% of LSIL, 84.38% of HSIL, and 100% of ASCH.

Table 2. Characteristic of HPV DNA Test and Histopathology

		DNA HPV			Total
		Not Detected	Low Risk	High Risk	
Histopathology	CIN 1	8	4	38	50
	CIN 2	3	-	23	26
	CIN 3	1	2	16	19
	Non CIN	32	1	10	43
Total		44	7	87	138

The accuracy and screening parameter of liquid-based cytology, HPV DNA test, and co-testing of liquid-based cytology and HPV DNA were analyzed by 2 x 2 table and resulted the accuracy parameter: sensitivity, specificity, positive predictive value, and negative predictive value. This study has results of sensitivity of liquid-based cytology, HPV

DNA, and co-testing of liquid-based cytology and HPV DNA as 88.54%, 81.25%, and 94.79% respectively; and positive predictive value as 75.89%, 89.66%, and 77.12% respectively. On the other hand, there were poor specificity results (35.71%) in both liquid-based cytology and co-testing (Table 3).

DISCUSSION

From the diagnostic value we obtained, we concluded that the highest sensitivity is the co-testing of liquid-based cytology and HPV DNA (94.79%); compared to single screening method of liquid-based cytology (88.54%) and HPV DNA (81.25%); even though the sensitivity of 88.54% is decent as a precervical cancer screening tool. This sensitivity of liquid-based cytology was in accordance with other study conducted by Oh et al in 2002 and Beerman et al in 2009 which stated that the sensitivity of liquid-based cytology was 92% and 96.24%, respectively.^{5,10} There was a wide range sensitivity of cytology-based screening as this procedure was operator-dependent, cytologist and pathologist. In this study, the operator bias was minimalized as the cytology sample was collected by the same experienced doctor. The poor specificity in liquid-based cytology (35.71%) is not consistent compared to the previous studies because the high false positive rate in this study which might be caused by error in interpreting the cytology result and the small proportion of non CIN result compared to CIN result. Nevertheless, this result not correlated to the purpose of this study which aims for screening the precervical cancer lesion as the specificity corresponds to the

Table 3. Accuracy of Liquid-Based Cytology, HPV DNA, and Co-Testing as Screening Tool

Diagnostic Parameter	Pre Cervical Cancer Lesion Screening		
	LBC	HPV DNA	LBC and HPV DNA
Sensitivity	88.54% (95% CI 80.42 - 94.14 %)	81.25% (95% CI 72 - 88.49 %)	94.79% (95% CI 88.26 - 98.29%)
Specificity	35.71% (95% CI 21.55 - 51.97%)	78.57% (95% CI 63.19 - 89.7%)	35.71% (95% CI 21.55 - 51.97%)
Positive Predictive Value	75.89% (95% CI 71.3 - 79.95%)	89.66% (95% CI 82.81 - 93.97%)	77.12% (95% CI 72.81 - 80.93%)
Negative Predictive Value	57.69% (95% CI 40.66 - 73.08%)	64.71% (95% CI 54.01 - 74.11%)	75% (95% CI 53.83 - 88.53%)
Positive Likelihood Ratio	1.38 (95% CI 1.09 - 1.75)	3.79 (95% CI 2.11 - 6.82)	1.47 (95% CI 1.17 - 1.86)
Negative Likelihood Ratio	0.32 (95% CI 0.16 - 0.64)	0.24 (95% CI 0.15 - 0.37)	0.15 (95% CI 0.06 - 0.38)

diagnostic purpose while sensitivity is the important value for the screening program to encompass as much as possible of the positive precervical cancer lesion patient.

In the HPV DNA, there was sensitivity of 81.25% and specificity of 78.57%. The sensitivity was slightly below the previous study of HPV DNA which the sensitivity of HPV DNA ranged 86 - 97.4%.^{7,11-13} The discrepancy of sensitivity in this study might be caused by the proportion of Non NIS and NIS 1 is 67.4% while the NIS 2+ is 32.6%; this situation could conduce the lower sensitivity since HPV DNA reached the good sensitivity in NIS 2+ as the cut-off point.^{7,8,14} Moreover, there was 7.9% samples with age below the 30 years old, where the HPV DNA is not recommended to be performed to women < 30 years old reckoned the high infection and regression rate in that population. In the perspective of liquid-based cytology, there were negative, ASCUS and LSIL result (72.14%) compared to 27.86% of HSIL; while Wheeler et al in 2014 reported the HPV DNA type 16 and 18 was detected respectively in 3.6% and 1.5% of negative result, 23.3% and 1.7% of ASCUS result, 32.5% and 19.6% of LSIL result; compared to 57.5% and 62.2% of ASCH, and 71.6% and 58.7% of result.¹⁵ Furthermore, the low sensitivity of HPV DNA could be caused by high false negative which might be caused by several factors, for instance the detection assay which not covers some type of HPV DNA, low titer or copy in HPV, inadequacy of specimen including the DNA quality, cytology sample with low abnormal cell, and error of pathologist.¹⁶

The co-testing of these two screening methods increased the sensitivity as much as 6.25% and 13.54% of liquid-based cytology and HPV DNA, respectively. The increased sensitivity was also accompanied with decreased false negativity of these two screening methods. In the clinical practice, these parameters will implicate the longer period for the next follow-up screening. Low specificity in liquid-based cytology and co-testing correspond to the high false positive which might be caused by error in cytology result. One of the drawbacks of this study is the absence of notation of other risk factor in medical record to exclude the situation which might influence the false negative and false positive; and also other demographic factors.

CONCLUSIONS

This co-testing test improves the sensitivity as well as negative predictive value, and positive predictive value of liquid-based cytology and HPV DNA. This result implies that this co-testing test could be one of the options of precervical cancer lesion screening in secondary or tertiary health center in Indonesia reckoned of its high cost, approximately Rp 1.200.000,-. Further studies regarding the cost effectiveness in this co-testing test since, despite of its high cost, it will implicate the longer period for the next follow-up screening until 3 - 5 years follow up.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136(5): E359-86.
2. ICO HPV Information Centre. Human Papillomavirus and Related Diseases Report. HPV Inf Cent. 2017; 1: 1-60.
3. Aziz MF. Gynecological cancer in Indonesia. *J Gynecol Oncol*. 2009; 20: 8-10.
4. Denny L. Cytological screening for cervical cancer prevention. *Best Pract Res Clin Obstet Gynaecol* [Internet]. 2012; 26(2): 189-96. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51706548>
5. Beerman H, van Dorst EBL, Kuenen-Boumeester V, Hogenboom PCW. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. *Gynecol Oncol* [Internet]. 2009; 112(3): 572-6. Available from: <http://dx.doi.org/10.1016/j.ygyno.2008.12.012>
6. Andrijono. Kanker Serviks. 4th ed. Jakarta: Divisi Onkologi Departemen Obstetri-Ginekologi Fakultas Kedokteran Universitas Indonesia; 2012. P1 - 61
7. Mayrand M-H, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer. *N Engl J Med* [Internet]. 2007;357(16):1579-88. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa.071430>
8. Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. *AIDS* [Internet]. 2013; 27(4): 607-15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23079814>
9. Lin H, Huang Y, Wu H, Kao J. Method for Testing for Human Papillomavirus Infection in Patients with Cervical Intraepithelial Disease. 2004; 42(1): 366-8.

10. Oh J, Shin H, Gong G, Sohn JH, Khang SK. Diagnostic accuracy of conventional Pap test, liquid-based cytology and human papillomavirus DNA testing in cervical cancer screening in Korea: a meta-analysis. *Kor J Epidemiol.* 2008; 30: 178-87.
11. Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al. Evaluation of Human Papillomavirus Testing in Primary Screening. *JAMA.* 2002; 288(14): 1749-57.
12. Dillner J, Rebolj M, Birembaut P, Petry K-U, Szaewski A, Munk C, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *Br Med J [Internet].* 2008; 337 (oct131): a1754-a1754. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.a1754>
13. Petry K-U, Menton S, Menton M, van Loenen-Frosch F, de Carvalho Gomes H, Holz B, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer [Internet].* 2003; 88(10): 1570-7. Available from: <http://www.nature.com/doi/10.1038/sj.bjc.6600918>
14. Griffiths M. Screening for cervical cancer in developing countries. WHO. 2002; 984.
15. Wheeler CM, Hunt WC, Cuzick J, Langsfeld E, Robertson M, Castle PE. The influence of type-specific human papillomavirus infections on the detection of cervical precancer and cancer: A population-based study of opportunistic cervical screening in the United States. *Int J Cancer.* 2014; 135(3): 624-34.
16. Jastania R, Geddie WR, Chapman W, Boerner S. Characteristics of apparently false-negative digene hybrid capture 2 high-risk HPV DNA testing. *Am J Clin Pathol.* 2006; 125(2): 223-8.

Case Report

Hysterectomy to the Unicornuate Uterus Suffering of Hematometra

Histerektomi pada Unicornuate Uterus dengan Hematometra

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Abstract

Objective: Unicornuate uterus with rudimentary cavity is an extremely rare Mullerian duct anomaly. It is frequently misdiagnosed or under treated, since women who suffer from this condition tend to be asymptomatic. We aimed to report this interesting case and review the available background literature.

Methods: Case report.

Case: A thirty two-year-old nulligravid woman was presented with severe abdominal pain. Laparoscopic surgery demonstrated unicornuate uterus with rudimentary cavity and hematometra. Partial hysterectomy was conducted to the right rudimentary uterus.

Conclusion: Thorough diagnosis is essential to prevent the complications of unicornuate uterus. Unicornuate uterus with rudimentary cavity is associated with increased rate of pregnancy complications such as preterm labor and fetal malpresentation. Pregnancy can also occurred on the rudimentary cavity and leads to recurrent pregnancy loss. Laparoscopy is essential for confirmatory diagnosis. Surgical intervention should be considered as the first line therapy to avoid associated morbidity.

[Indones J Obstet Gynecol 2017; 5-4: 246-249]

Keywords: hematometra, hysterectomy, unicornuate uterus

Abstrak

Tujuan: Melaporkan kasus kelainan bawaan pada uterus dan membahas literatur terkait. Unicornuate uterus dengan rongga rudimenter merupakan kasus yang sangat jarang pada kelainan duktus Mullerian. Kasus ini sering tidak terdiagnosis sehingga tidak mendapatkan penanganan yang sesuai terutama dikarenakan sebagian besar pasien tidak memiliki keluhan.

Metode: Laporan kasus.

Kasus: Tiga puluh dua tahun nulligravida datang dengan keluhan utama nyeri hebat pada perut bagian bawah. Laparoskopi menunjukkan unicornuate uterus dengan rongga rudimenter dan hematometra sisi kanan. Histerektomi parsial dilakukan pada uterus rudimenter tersebut.

Kesimpulan: Diagnosis menyeluruh diperlukan untuk mencegah komplikasi pada unicornuate uterus. Komplikasi yang berhubungan dengan unicornuate uterus antara lain kelahiran prematur dan malpresentasi. Kehamilan pada kavum yang rudimenter juga dapat terjadi dan mengakibatkan gagalnya kehamilan. Laparoskopi adalah alat utama untuk memastikan diagnosis. Intervensi bedah sebaiknya menjadi lini pertama untuk mencegah morbiditas.

[Maj Obstet Ginekologi Indones 2017; 5-4: 246-249]

Kata kunci: hematometra, histerektomi, unicornuate uterus

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INTRODUCTION

Congenital uterine anomalies were found in 5.5% of unselected population, 8.0% of infertile women, and 13.3% in women with a history of miscarriage, and 24.5% in those with miscarriage and infertility.¹⁻³ Unicornuate uterus is a rare congenital anomaly of the female reproductive system, resulting from partial development of one-out-of-the-two Mullerian ducts.¹ It causes numerous gynaecologic and obstetrical complications², and it is also associated with increased rate of preterm birth, fetal malpresentation and gestation in the rudimentary cavity.² The European's Society of

Human Reproduction and Embryology (ESHRE)/European's Society for Gynaecological Endoscopy (ESGE) has adopted a new classification system², in which according to this new system, unicornuate uterus (U4) incorporates all cases of unilateral formed uterus, and the contralateral part could be either incompletely formed or absent (Figure 1).^{2,4,5} Unicornuate uterus with a rudimentary (functional) cavity (U4a) is characterized by the presence of a communicating or non communicating functional contralateral horn.^{2,5} Since women with this condition are asymptomatic, the true incidence has not been yet determined.³ However, it has been reported that between 0.1% of the unselected population,

unicornuate uterus is significantly more common in women with a history of miscarriage, miscarriage in association with infertility, and/or infertility alone.^{1,2} This malformation is associated with the presence of a rudimentary horn in 74-90% of cases.^{1,6} Approximately, 25% of these horns are characterized by the presence of a cavity with functional endometrium, which does not communicate with the main cavity of the contralateral unicornuate uterus.⁶ We presented a case of unicornuate uterus with rudimentary cavity and non communicating horn.

CASE

A 32-year-old nulligravid woman was referred to

the hospital with chief complaint of severe progressive worsening abdominal pain. She had been married for 1 year. Physical examination revealed normal vagina and cervix. Abdominal ultrasound revealed double uterus. Laboratory examination demonstrated hemoglobin of 14.8 g/dl, hematocrit of 36.5%, white blood cell count of 7300/mm³, and Ca-125 of 17.41 U/ml. Chest X-ray and ECG were normal. A month prior to laparotomy, a laparoscopy was done, and we found a unicornuate uterus with right rudimentary cavity and non communicating horn. Partial hysterectomy was performed to the right rudimentary uterus with hematometra. Both ovaries and the fallopian tubes were within normal limits.

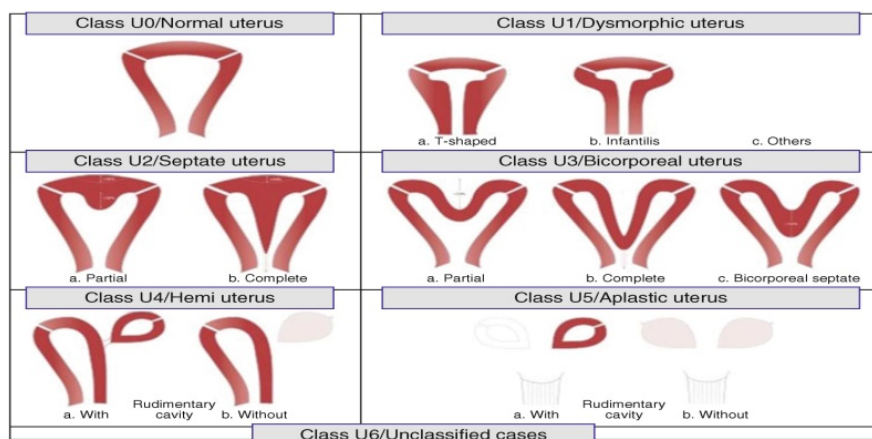


Figure 1. The ESHRE/ESGE classification of uterine anomalies (Adapted from Grimbizis, et al.)^{1,3}



Figure 2. Show the topography between left uterus and right rudimentary uterus (Laparoscopic view)

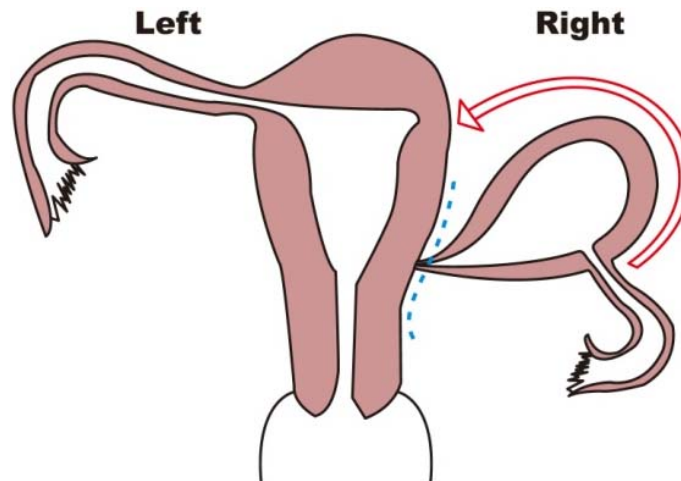


Figure 3. Schematic representation of hysterectomy



Figure 4. Partial hysterectomy perform to the right rudimentary uterus (Laparotomy)

DISCUSSION

Unicornuate uterus of the Mullerian duct is a congenital anomaly resulting from a rudimentary horn.^{1,2,3} The developmental anomaly is classified according to its relation with the uterine cavity. The pathogenesis of Mullerian duct abnormality has been well established, yet the etiology remains unknown. The etiologies are multifactorial, including genetic and environmental factor. The embryologic tendency of dominance of the right-sided unicornuate uterus remains unelucidated.

The true incidence of female congenital malformations is unknown.¹ The use of diagnostic tools with different accuracy, the subjectivity in the criteria used for diagnosis and classification of the anomalies as well as the drawbacks of the existing classification systems represent the main

biases for the actual burden. The recently introduced ESHRE/ESGE classification of female genital anomalies aims to provide a more suitable classification system for an accurate, clear, and simple categorization of female genital anomalies associated with the clinical management.⁴ Diagnosing these anatomical malformations is not an easy task; hysteroscopy, HSG and 2D-transvaginal ultrasound are suboptimal approaches because most of these tests do not allow evaluation of the external contour of the uterus. MRI has been reported to have a high accuracy rate in diagnosing unicornuate uterus.⁶ Unicornuate uterus can be found incidentally during gynecologic examination or because of abdominal pain as seen in our case.

One possible cause of abdominal pain in this patient is uterine distention due to blood accumu-

lation in the noncommunicating cavity of the rudimentary horn (hematometra).^{1,6} Excision of the uterine horn without a functioning endometrium attached to the unicornuate uterus merely to enhance obstetric outcomes is not warranted. When there is no functioning endometrium, no intervention is warranted. However, if functioning endometrium is present, excision should be considered particularly when complicated with hematometra. Surgical removal of the noncommunicating horn is commonly performed particularly on functional endometrium to prevent endometriosis and pregnancy within the horn. Hadisaputra, et al (2016) reported a successful pregnancy after hysterectomy of bicorporeal uterus, delivering a healthy baby of 3260 grams.⁷ In this case, removal of the functional cavity resulted in relief of abdominal pain.

CONCLUSION

This case was classified as class U4a - unicornuate uterus with a right-side rudimentary (functional cavity) and hematometra. It is associated with increased rate of preterm birth, fetal malpresentation and gestation in the rudimentary cavity. Surgical intervention is proven to be a successful approach in the treatment of this congenital Mullerian anomaly. Further investigation to assess whether the removal of rudimentary cavity of unicornuate uterus might increased the rate of successful pregnancy is required.

REFERENCES

1. Grimbizis GF, Campo R, Tarlatzis BC, Gordts S, et al. Female Genital Tract Congenital Malformation: Classification, Diagnosis, and Management. London: Springer. 2015; 15-45.
2. Chan YY, Jayaprakasan K, Tan A, et al. Reproductive outcomes in women with congenital uterine anomalies: A systematic review. *Ultrasound Obstet Gynecol.* 2011; 38: 371-82.
3. Chan YY, Jayaprakasan K, Tan A, et al. The prevalence of congenital uterine anomalies in unselected and high risk populations: A systematic review. *Hum Reprod Update.* 2011; 17(6): 761-77.
4. Grimbizis GF, Gordts S, Sardo ADS, et al. The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. *Hum Reprod.* 2013; 28: 2032-44.
5. Pados G, Tsolakidis D, Athanatos D, et al. Reproductive and obstetric outcome after laparoscopic excision of functional, non-communicating broadly attached rudimentary horn: A case series. *Eur Obstet Gynecol Reprod Biol.* 2014; 182: 33-7.
6. Vaz SA, Dotters K, Kuller JA. Diagnosis and Management of Congenital Uterine Anomalies in Pregnancy. *Obstet Gynecol Surg.* 2017; 72(3): 194-01.
7. Hadisaputra W, Pramayadi CT, Berguna JSN, et al. Successful Pregnancy After Hysterectomy in a Case of Bicorporeal Uterus With Hematometra. *J Min Invasive. Gynecol.* 2016; 23(6): 853-4.

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