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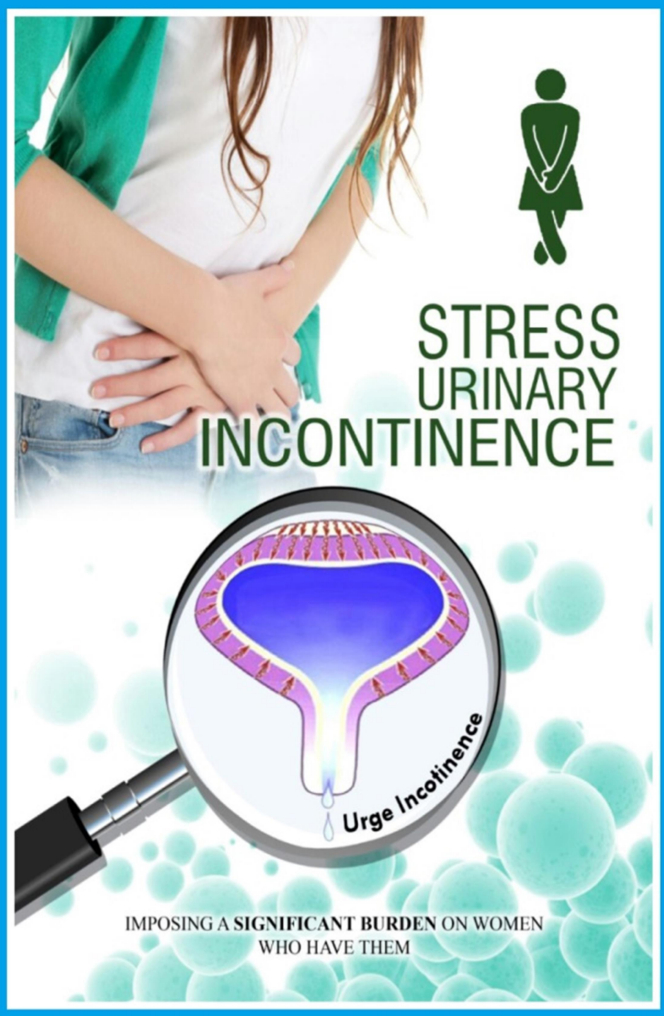

Editorial

Research Articles

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EDITORIAL

RESEARCH ARTICLE

Research Article

Effectiveness of Oral Prebiotics as Adjuvant Theraphy in Reproductive Aged Women with Vaginal Discharge

Efektivitaas Probiotik Oral sebagai Terapi AjuvanKeputihan pada pasien usia reproduksi

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Abstract

Objective: To investigate the efficacy of oral probiotics and prove the high proportion of cure and satisfaction levels of post-treatment patients with a combination of antimicrobial-probiotic oral Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 compared to a combination of antimicrobial-placebo in the treatment of reproductive aged patients with vaginal discharge in the outpatient obstetrics and gynecologic clinic in Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia and Arifin Achmad Regional Hospital Pekanbaru, Riau, Indonesia.

Methods: This was a randomized, double-blind, placebo-controlled trial involving 50 subjects consisting of reproductive aged women. Data were collected using syndromic approach, probiotics were given as an adjuvant for standard antimicrobial therapy versus placebo as control, response was recorded 4 weeks later, for cure proportion and satisfaction level. Statistical analysis was performed to assess the variables. Interim analysis with conditional power assesment and futility testing were performed at midway due to insufficient sample size. Research was approved by Ethics Commitee for Health Researches Faculty of Medicine University of Indonesia Dr. Cipto Mangunkusumo Hospital in March 2016.

Results: A total of 50 subjects participated in this study and analyzed (25 subjects in each group), cure proportion 56% (14) of the treatment and 60% (15) on the control group, with relative risk of 1.1, Chi-square test p value 0.77 (95% CI; 0.57 to 2 , 11). High satisfaction level (score ≥67) was higher in the placebo (52.6%, 10 subjects) compared to probiotic group (47.4%, 9 subjects), p value 0.65 (≥0.05). Conditional power and futility testing curve, revealed Z = -0.2865, conditional power 0.11 to 0.13, and futility index of 0.87 to 0.88, equals to low possibility of statistical significance with full sample size (84).

Conclusion: There was no clinical and statistical difference in the proportion of cure rate and the level of satisfaction in patients of probiotics vs placebo groups after treatment for 4 weeks. The initial hypothesis of higher proportion of the cure rate in the treatment group still cannot be excluded, due to insufficient samples.

[Indones J Obstet Gynecol 2018; 6-1: 3-9]

Keywords: bacterial vaginosis, lactobacillus reuteri RC-14, lactobacillus rhamnosus GR-1, randomized double blind controlled trial, trichomoniasis, vaginal discharge, vulvovaginal candidiasis

Abstrak

***Tujuan**: Mengetahui efektivitas klinis dan dibuktikan tingginya proporsi kesembuhan dan tingkat kepuasan pascaterapi pasien kombinasi antimikroba-probiotik oral Lactobacillus rhamnosus GR-1 dan Lactobacillus reuteri RC-14 dibanding kombinasi antimikroba-placebo pada pengobatan pasien usia reproduksi dengan keputihan di poliklinik rawat jalan obstetrik dan ginekologi Rumah Sakit Dr. Cipto Mangnukusumo (RSCM) dan Rumah Sakit Umum Daerah (RSUD) Arifin Achmad Pekanbaru, Riau.*

***Metode**: Penelitian ini merupakan penelitian uji klinis acak tersamar ganda dengan 50 subjek perempuan usia reproduksi, dengan 25 subjek pada setiap kelompok. Data dikumpulkan dengan pendekatan sindromik, pemberian probiotik sebagai ajuvan terapi antimikroba standar versus plasebo sebagai kontrol, dicatat respon terapi 4 minggu. Analisis statistik dilakukan untuk menguji variabel. Analisis interim, conditional power dan uji futilitas dilakukan di tengah penelitian karena jumlah sampel awal tidak tercapai. Penelitan ini sudah lolos kaji etik dan mendapat persetujuan pelaksanaan dari Komite Etik Penelitian Kesehatan FKUI-RSCM pada bulan Maret 2016.*

***Hasil**: Sebanyak 50 subjek dapat terkumpul dan dianalisa (25 subjek pada tiap kelompok), proporsi kesembuhan 56% (14) pada kelompok perlakuan dan 60% (15) dari kelompok kontrol, dengan risiko relatif sebesar 1,1, nilai p 0,77 (95% CI; 0,57-2,11). Proporsi tingkat kepuasan tinggi (skor ≥67) lebih besar pada kelompok plasebo (52,6%, 10 subjek) dibanding kelompok probiotik sebesar 47,4% (9 subjek), dengan p 0,65 (≥0,05). Analisis conditional power dan uji futilitas, diperoleh nilai Z = -0.2865, conditional power 0,11-0,13 dan indeks futilitas 0,88-0,87, sehingga kemungkinan kecil penelitian akan bermakna bila dilanjutkan hingga tercapai sampel total (84).*

***Kesimpulan**: Tidak ditemukan perbedaan proporsi yang bermakna secara klinis maupun statistik pada kesembuhan maupun kepuasan pada kelompok probiotik vs plasebo setelah terapi selama 4 minggu, namun hipotesis awal proporsi kesembuhan kelompok probiotik lebih tinggi belum bisa ditolak, karena jumlah sampel belum memadai.*

[Maj Obstet Ginekol Indones 2018; 6-1: 3-9]

***Kata kunci**: bakterial vaginosis, keputihan, lactobacillus reuteri RC-14, lactobacillus rhamnosus GR-1, randomized double blind controlled trial, trichomoniasis, vulvovaginal candidiasis*

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INTRODUCTION

Vaginal discharge is the most frequent gynecological complaint found in primary health care, with its annual visit amounted to 10 millions/year in the United States in 2004[1], which can be classified as normal or abnormal.[2] Abnormal vaginal discharge may cause discomfort, reduced productivity, and even serious reproductive complications in both pregnant and non pregnant women, if left untreated.[2] The most common cause of abnormal vaginal discharge is bacterial vaginosis (BV) in 22-50% cases, vulvovaginal candidiasis (VVC) in 17-39% cases, and trichomoniasis in 4-35% cases.[2]

The condition is caused by imbalance of normal vaginal flora (i.e. reduced lactobacilli and increased comensal/pathogenic microbes such as G. vaginalis, Mycoplasma hominis, Bacteroides species, Peptostreptococcus species, Fusobacterium species, Prevotella species, and Atopobium vaginae) in the vagina that caused increased vaginal pH, reduced protection of vaginal mucosa, and increased probability of invasion from other microbes that may result in abnormal vaginal discharge.[2,3]

Several risk factors that may contribute to the condition include age below 25 years of age or being older than 40 years old, uncircumsized male sexual partner, black ethnicity, sexual partner more than one, changing sexual partner within the last 30 days, female to female sexual encounter, immunodeficiency (e.g. HIV), diabetes mellitus, poor vaginal hygiene, sexual intercourse more than once a week, after vaginal delivery or postabortal patients, and vaginal douching.[4-8]

The diagnostic flowchart above is practical to be used in general everyday primary health outpatient service without the use of other diagnostic tools. This approach is known as the syndromic approach.[9]

Probiotics are defined as live microorganisms that may confer health benefit to the human host if given in sufficient amount.[10] Studies have already proved the effectiveness of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 either as adjuvant or main treatment of vaginal discharge caused by BV, VVC, notably by Anukam et al in 2006, where the treatment group of oral probiotics has increased rate of cure (88% vs 40%) compared to controls, in a randomized double

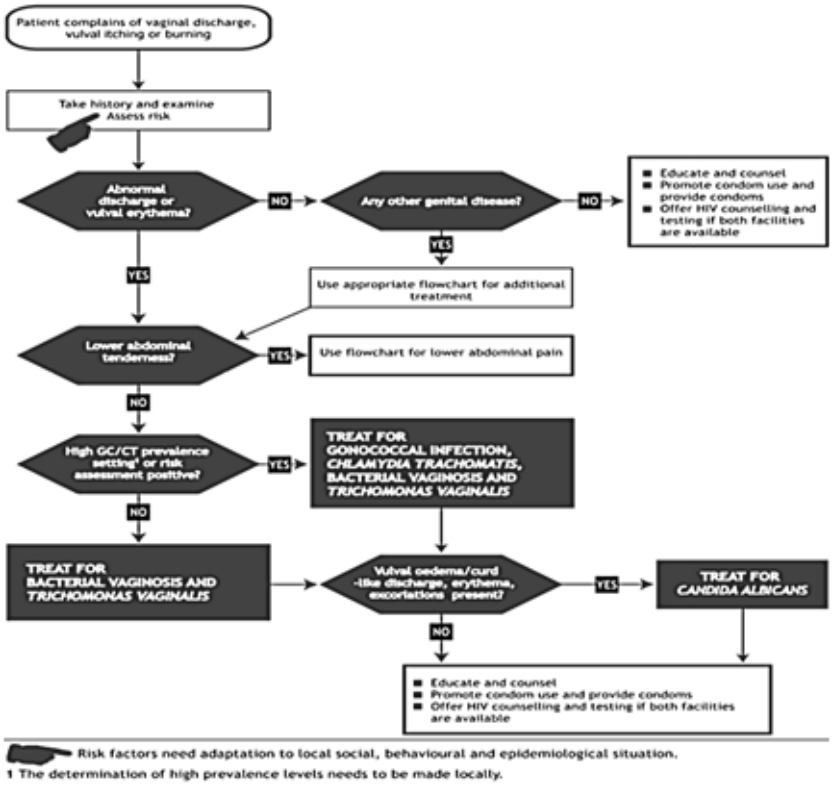

Figure 1. WHO Syndromic Approach Flowchart for Vaginal Discharge

blind controlled trial study[11] or other successful trials to prove the effectiveness of oral probiotics in skim milk form (Reid et al) or capsules (Martinez et al) to cure vaginal discharge caused by VVC.[10,12]

Trials involving the use of oral probiotics for vaginal discharge in Indonesia have never been conducted. This study is determined to see if the use of similar oral probiotic containing Lactobaci-llus rhamnosus GR-1 and Lactobacillus reuteri RC-14 will confer similar benefits for Indonesian women as other studies above.

OBJECTIVES

In this study, the proportion of patients of reproductive age cured clinically of vaginal discharged was significantly higher on combined antimicrobes- oral probiotics Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 compared to combined antimicrobes-placebo after 4 weeks treatment. Therefore the goal was to acknowledge the clinical effectiveness and prove the high proportion of cure and satisfaction levels of post-treatment patients with a combination of antimicrobial-probiotic oral Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 compared to a combination of antimicrobial-placebo in the treatment of patients of reproductive age with vaginal discharge in the clinic outpatient obstetrics and gynecology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, and Arifin Achmad Regional Hospital Pekanbaru, Riau, Indonesia.

METHODS

This was a randomized, double-blind, placebo-controlled trial with initial sample size of 84 subjects, and by consecutive sampling, only 50 subjects were able to be analyzed with target population of reproductive age women who visited with complain of vaginal discharge to outpatient clinic at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia and Arifin Achmad Hospital Pekanbaru, Riau, Indonesia. Subjects age are between 15-49 years old. Inclusion criteria in this study were; reproductive age women, with vaginal discharge complain, married or had had sexual intercourse, and signed consent to be included in the study. Exclusion criteria were physiologic vaginal discharge, consuming antibiotics or corticosteroid, had HIV, diabetes mellitus, currently pregnant, postpartum/post-abortion in the past 40 days, menstruation, sexual partner more than one, cervical polyp, malignancy, urogenital fistula, allergic reaction, menopausal women, allergy to the antimicrobes or probiotics used in this study.

After consenting to the study, the subjects then underwent history taking and physical examination by using a special case report form, by syndromic approach. The patient was then given standard antimicrobes according to the suspected findings (BV, VVC, Trichomoniasis, or combined) and randomized to have oral probiotics containing each $2{,}5x10^9$ Lactobacillus rhambosus GR-1 and Lactobacillus reuteri RC-14, or placebo by contacting the pharmacy prior to administration. The adjuvan had already packaged in a way that is difficult to differentiate between treatment and placebo (blinding) by the central pharmacy. The patient was then instructed to return for visit after 4 weeks of daily probiotics.

All statistical analyses were performed using SPSS17 for Windows. The Chi Square test was used to analyze the difference of proportion of cure and the level of satisfaction between the groups. Interim analysis, conditional power and futility analysis was performed, since the sample size was lower to determine the probability of significancy had the study continued to full sample size.

RESULTS

A total of 50 subjects were recruited in this the study. Interim analysis was performed, with O'Brien-Flemming at sample size 24 and 50 women, with $p=1$ ($p>0.05$) on both analysis, corresponds to insignificance results We performed conditional power and futility analysis. The z score the time of 50 sample size is -0.2865, which equal to conditional power of 0.11-0.13 corresponding to futility index of 0.87-0.89, therefore the study will less likely to achieve statistical significance even if continued to full sample size (futility index > 0.8).

The subjects age are between 22-48 years old reproductive aged women. The age distribution followed the normal distribution curve on all respondent (Saphoro-Wilk; $p = 0.29$). Age of the subjects were 15-24 years old (10%), 25-34 years old (43%), 25-44 years old (44%). The mean age of treatment group was 35.7 years old (SD 6.17) and 34.6 years old (SD 7.17) on the treatment and control group respectively. Most of the subject age

were between 35-44 years old on treatment (48%) and control (40%) group.

Majority of the subjects on treatment group was employee (64%). No multiple sexual partners was noted on both groups. The frequency of sexual intercourse was more than 1 time per week on both group 84% and 88% on treatment and control group respectively, vaginal douching habit was found on 40% subject on both groups, no subject was found to have multiple sexual partner.

Proportion of Cure

In this study, the cure proportion of all subjects was 58%. The proportion of cure was 56% and 60% on treatment and control group respectively, with relative risk on the uncured subjects was 1.1 (p=0.77, 95% CI = 0.57-2.1) as seen on Table 1, also the following calculation below.

Table 1. Cure Distribution on Treatment and Control

Groups	Not cured		Cure		Total	
	n	%	n	%	n	%
Treatment	11	44	14	56	25	50
Expected count	10.5		14.5			
Control	10	40	15	60	25	50
Expected count	10.5		14.5			
Total	21		29		50	100

$$\text{Experiment Event Rate (EER)} = \frac{a}{a+b} = 0.44$$

$$\text{Control Event Rate (CER)} = \frac{c}{c+d} = 0.4$$

$$\text{Relative Risk (RR)} = \text{EER} / \text{CER} = 0.44/0.4 = 1.1$$

Satisfaction level was recorded using specific form based on treatment satisfaction Questionnaire for Medication (TSQM VERSION II). The most common satisfaction level in treatment group is on the medium level (score 34-66), that is 44% (CI 90%, 23.1-64.9), followed by high satisfaction level (36%) and lastly is low satisfaction level (20%). On the control group, however, the majority on satisfaction level is at high level (score ≥67) on 40 % of subjects (CI 95%, 19.4-60.6), followed by medium level (32%) and low level of satisfaction (28%).

On comparison (Table 2), low and high satisfaction level (score 0-33) is mostly seen on control (placebo) group (58.3 and 52.6% respectively) compared to that of treatment (probiotics) group (41.7 and 47.4% respectively), while on the medium satisfaction level mostly observed on treatment group (57.9%) compared to that of control (42.1%). Statistical test revealed p 0.65 ($p \geq 0.05$), corresponds to no significant difference of treatment and control (placebo) group.

On the sexual intercourse analysis, the respondents that were cured mostly had sexual intercourse frequency of more than one time per week, as much as 86.2%. Similarly, that uncured subjects had similar frequency of sexual intercourse as much as 85.7%. The result was statustically analyzed and reveled $p = 1.0$ ($p \geq 0.05$) and relative risk of 1, corresponds to insignificant difference between the groups.

Multivariate analysis for confounding variable was not performed in this study due to no ethnical difference of both treatment (probiotics) and control (placebo) group and also of no apparent significant difference on sexual intercourse frequency analysis, therefore was not fulfilling the requirement of ($p < 0.25$) significance level to be included in multivariate analysis.

Table 2. Comparative Proportion of Treatment Satisfaction Level of Treatment (Probiotics) and Control (Placebo) Group

Satisfaction Level	Treatment (Probiotics)		Control (Placebo)		Total		p value
	n	%	n	%	n	%	
Low	5	41.7	7	58.3	12	100	
Medium	11	57.9	8	42.1	19	100	0.65
High	9	47.4	10	52.6	19	100	
Total	25	50.0	25	50.0	50	100	

The sample size for treatment and control group was similar (25 subject each), this size was smaller to initial sample size of total 84 subjects, corresponds to lower power as have been discussed earlier on the result. The subjects were mostly at the age of 35-44 years old and normally distributed. Difference in demographic data was seen on the education level, whereas on the treatment group, half of the subjects had duration of education of more than or equal to 13 years, while on the control group, duration of education was equally distributed on two subgroups (duration of education of 10-12 years and more than or equal to 13 years) as much as 36% on each subgroups. On both groups, we did not find any subject with multiple sexual partner and frequency of sexual intercourse on both groups were more than once a week (probiotics 84%, placebo 88%). Subjects on the treatment group were mostly working (64%) reversely different with that of the placebo group. There was no side effect or adverse incident related to the study procedure in this study.

We found that the proportion of vaginal discharge patients that were cured was mostly on the control (placebo) group as much as 15 subjects (60%) compared to the treatment (probiotics) group as much as 14 subjects (56%). However this difference was only for 1 subject, with effect difference of 4%, and relative risk calculation of 1.1. Based on these result, (effect size 4% of 20% expected initially), these results were statistically and clinically insignificant. Moreover, Chi Square test revealed p 0.77 (>0.05), thus the difference between the groups was insignificant.

From the satisfactory level, we found that the placebo group had more satisfactory level according to subjects compared to the probiotics groups, and statistical test did not reveal significant difference of three satisfaction level between the groups (p 0.65).

On the analysis based on frequency of sexual intercourse, the cure rate was higher on group with more than one time sexual intercourse per week (86%) compared to 13.8% on the other group. Theoritically, frequency of sexual intercourse was considered to be connected to vaginal ecosystem and increased risk of BV, by reducing colonization of H2O2 forming lactobaccili or to increase BV related species such as Gardnerella vaginalis.[13] Contradictively similar result was reported by Foxman on his case control study in 1990, including 85 women, that stated sexual intercourse frequency of more than one per week is related to increased risk of VVC with OR 1.73 to 2.98 increasing with frequency per week.[14] However, a cross sectional study in Indonesia by Dwiana Ocviyanti et al in 2010 on 492 women aged 15-50 years old, regarding risk factors for BV did not mention that sexual intercourse frequency per week to be considered a risk factor, instead that it was found that uncircumsized male (OR 6.25) and age of more than 40 years old (OR 3.15).[8] While other observational cohort study in 2011 revealed that digital insertion sexual act is related to increased colonization of Gardnerella vaginalis and the researchers also stressed on the notion that sexual intercourse frequency indeed did not relate with increased risk of BV.[13] So we can conclude that frequency of sexual intercourse per week did not relate with increased risk of vaginal discharge on both groups. In this study, there was also no ethnical difference between the subjects therefore was not included in analysis since all the subjects was of Asian origin.

Insufficient sample in this study was due to difficulty in fulfilling the initial 84 subjects during the study process, particularly on Arifin Achmad Hospital, resulting in subjects only collected from Dr. Cipto Mangunkusumo Hospital (50 subjects, 25 in each group). The difficulty was due to luckiness of patients that fulfill the inclusion criteria for the study and high drop out particularly on Arifin Achmad Hospital. However, we predicted that this luckiness of subjects, will not affect the outcome had the study had sufficient sample size was achieved, as with futility index testing of 0.87-0.89. Addition of sample up to initial size of 84 subjects will not change the result to be statistically significant, since it was not significant in 50 subjects.

Anukam et al and Martinez et al had conducted similar studies in 2006 and 2009, respectively, with the former was on bacterial vaginosis patients and the latter was on candidiasis patients, which both yield considerably different results from both studies, 88% (p<0.001) cure rate on the former and less discharge (10.3% vs 34.6%, p=0.014) on the latter, which most probably due to tighter inclusion criteria (using Nugent criteria, sialidase enzyme, culture) and outcome analysis which was compared using culture, therefore resulting in more accurate outcome from only depending on

clinical-syndromic approach as applied in our study.[11,12] Sialidase enzyme is produced by anaerobic bacteria such as Prevotella and Bacteroides spp, that promotes bacterial adhesion toward vaginal epithelium and musinase activity, helping vaginal mucose invasion by BV related bacterias.[15] This enzymatic assessment is superior compared to Nugent and Amsel criteria with sensitivity of 88% (95% CI, 81 to 93%) and spesitivity of 95% (95% CI, 91 to 98%).[15]

This study used probiotics as adjuvant of standard antimicrobial treatment, therefore it is difficult to assess difference of cure on both groups, considering that antimicrobial treatment alone in this study (placebo group) was capable of resulting in 60% cure rate compared to treatment group, with effect size of 4%, far below expected of 20%. One literature also mentioned that standard metronidazole treatment as applied in this study for BV treatment based on CDC guideline 2015 alone may result in cure rate as much as 70%.[16]

Another weakness of this study, besides the humble syndromic-clinical criteria used, is also due to difficulty in collecting samples at the second hospital (Arifin Achmad Hospital Pekanbaru), whereas after 10 months of study near the expired date of probiotics used in this study, subjects fulfilling inclusion and exclusion criteria were only 4 samples, and none of them return for re-assessment (drop out).

Moreover, in this study, one of the possibilities of insignificant result of the study was due to the difference of interpretation of physicians assessing each subjects that are changing (due to resident's rotation) every month, albeit already trained by us, may contribute to variation of cure assessment from one physician or another. Therefore, there is a possibility of enhancing the interpretation had we use other objective means, such as photography documentation.

Therefore we may that insignificant comparison in proportion of cure on both groups in this study that is not different from one another is due to lackness of sample size, inaccurate inclusion criteria due to only using syndromic-clinical approach, and response assessment that was not confirmed by culture result such as previously mentioned similar studies.[11,12]

The results are potential to be studied further by tightening the inclusion criteria with Nugent and Amsel criteria, sialidase enzyme detection, or culture, to ensure that the clinical results observed are in accordance to laboratory confirmation for more objective assessments. This study is the first study in Indonesia done with double blind Randomized Clinical Trial to prove the clincial effectiveness of combined antimicrobes-oral probiotics Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 compared to antimicrobes-placebo for treatment of reproductive age women with vaginal discharge.

CONCLUSION

There was no clinical and statistical difference in the proportion of cure and the level of satisfaction in patients of reproductive age with vaginal discharge in the treatment with combination of antimicrobial-oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 compared to combination of antimicrobial-placebo after treatment for 4 weeks. However, in this study, the initial hypothesis of higher proportion of cure at the treatment group (probiotic) compared to placebo still cannot be excluded, due to insufficient samples collected.

REFERENCES

1. Mashburn J. Etiology, Diagnosis, and Management of Vaginitis. J Midwifery Won Heal. 2006: 423-30.
2. Beckmann CRB, Ling FW, Barzansky BM, Herbert WNP, Laube DW, Smith RP. Obstetrics and Gynecology. Baltimore, MD; Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
3. 14th ed. Philadelphia: Lippincott Williams & Wilkins; Berek Novak's Gynecol, 2007: 542.
4. Wilson J. Managing recurrent bacterial vaginosis. Sex Transm Infect. 2004; 80: 8-11.
5. Eckert LO. Acute Vulvovaginitis. N Engl J Med. 2006; 355: 1244-52.
6. Patel DA, Gillespie B, Sobel JD, Leaman D, Nyirjesy P, Weitz MV, et al. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: Results of a prospective cohort study. Am J Obstet Gynecol. 2004; 190: 644-53.
7. Cruickshank M, Hay I. The Management of Vulval Skin Disorders (Green Top Guideline) 2011 3/10/2012; (58):[1-23 pp.]. Available from: http://www.rcog.org.uk/files/rcog-corp/GTG58Vulval22022011.pdf.
8. Ocviyanti D, Rosana Y, Olivia S, Darmawan F. Risk factors for bacterial vaginosis among Indonesian women. Med J Indones. 2010; 19(2): 130-5.
9. WHO. Guidelines for the Management of Sexually Transmitted Infections. Switzerland: WHO Publications; 2003: 21-4.
10. Reid G, Jass J, Sebulsky MT, McCormick JK. Potential Uses of Probiotics in Clinical Practice. Clin Microbiol Rev. 2001; 16(4): 658-72.

11. Anukam K, Osazuwa E, Ahonkhai I, Ngwu M, Osemene G, Bruce AW, et al. Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14: randomized, double-blind, placebo controlled trial. Microbiol Infect. 2006; 8: 1450-4.
12. Martinez RCR, Franceschini SA, Patta MC, Quintana SM, Candido RC, Ferreira JC, et al. Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14. Lett Appl Microbiol 2008; 48: 269-74.
13. Mitchell C, Manhart LE, Thomas KK, Agnew K, Marrazzo JM. Effect of sexual activity on vaginal colonization with hydrogen-peroxide producing Lactobacilli and Gardnerella vaginalis. Sexual Trans Diseases. 2011; 38(12): 1137-44.
14. Foxman B. The epidemiology of vulvovaginal candidiasis: risk factors. Am J Public Health. 1990; 80(3): 329-31.
15. Bradshaw CS, Morton AN, Garland SM, Horvath LB, Kuzevska I, Fairley CK. Evaluation of a Point-of-Care Test, BVBlue, and Clinical and Laboratory Criteria for Diagnosis of Bacterial Vaginosis. J Clin Microbiol. 2005; 43(3): 1304-8.
16. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines (2015). MMWR Recomm Rep. 2015(24): 51-6.

EDITORIAL

Stress Urinary Incontinence (SUI): Conservative and Surgical Approach

Budi I Santoso

Stress urinary incontinence (SUI) is defined as the involuntary leakage of urine at exertion or increased abdominal pressure. It affects approximately 4-35% of women and impacts the quality of women's life.[1,2] The treatment for SUI can be divided into conservative and surgical approaches. Conservative treatment includes pelvic muscle exercise (PME) or incontinence pessaries. A pelvic muscle exercise known as Kegel is used for urge, stress, and mixed continence for strengthening the muscular components of urethral closure mechanism.[3] Meanwhile, duloxetine is believed to be effective in treating SUI.[4] Expert opinion stated that trial of anticholinergic drug in patients with mixed urinary incontinence can be reasonable at the availability of urge symptoms.[5]

For surgical procedure, there are several approaches including vaginal through mid-urethral sling, bladder neck sling, injection of urethral bulking agents, abdominal through Burch retropubic colpo-suspension. A meta-analysis revealed that mid-urethral slings were comparable with other procedures. Shorter operative duration, similar rate of perioperative complication, similar frequency of adverse effects on bladder, and shorter hospital stay were shown in patients choosing mid-urethral sling.[6] Therefore, mid-urethral sling has become one of the best choice for women with SUI desiring surgical treatment. However, only apical prolapse that should be treated with open abdominal sacrocolpopexy (Burch colposuspension).[7] In conclusion, conservative approach is still an option for SUI women refusing surgery and mid-urethral sling becomes a preferable technique for SUI due to the exception in SUI with apical prolapse.

References

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010; 29: 4.
2. Kane AR, Nager CW. Midurethral slings for stress urinary incontinence. Clin Obstet Gynecol 2008; 51: 124.
3. Hay-Smith J, Berghmans BK, et al. Adult conservative management. In: Incontinence, 4th Ed., Abrams P, Cardozo L, Khoury S, Wein A (Eds), Health Publications Ltd, Paris 2009: 1025.
4. van Kerrebroeck P, Abrams P, Lange R, et al. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG 2004; 111: 249.
5. Mariappan P, Ballantyne Z, N'Dow JM, Alhasso AA. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. Cochrane Database Syst Rev 2005: CD004742.
6. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2009: CD006375.
7. Maher CF, Qatawneh AM, Dwyer PL, et al. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. Am J Obstet Gynecol 2004; 190: 20.

Research Article

The Association between Menstrual Disorder and Work Disturbance among Employees

Hubungan Gangguan Menstruasi dan Gangguan Kerja pada Karyawati

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Abstract

Objective: To investigate the association between menstrual disorders including each menstrual cycle disorder, duration and volume of menstrual bleeding disorder, menstrual interval disorder, and another disorder that related to menstruation against disruption of work among employees.

Methods: This study used a cross sectional design. Sample randomization with winpepi® software for Windows 7®. Data analysis using SPSS 24® software for Windows 7®.

Results: A total of 150 subjects were recruited in this study. The prevalence of menstrual disorder was 87%, menstrual cycle disorder 3%. Menstrual volume disorder 31%, 15% menstrual abnormalities, 83% menstrual pain disorder and premenstrual syndrome 71%. Prevalence of work disturbance was 49% for mild disturbance, 47% for moderate disturbance and severe work disturbance by 4%. There was a relationship between menstrual volume disorder, hypermenorrhoea, and menstrual / dysmenorrhoea pain to occupational disruption among the employee at RSCM (p <0.001). The submission of the proposed leaves due to menstrual disorder in the proposed permit for 1 day by 73%.

Conclusion: The prevalence of severe work disturbance due to menstruation is not high but can lead to disruption in running jobs and activities. However, it is important to be a concern so that the employees get good management and care.

[Indones J Obstet Gynecol 2018; 6-1: 10-17]

Keywords: employee, menstrual leave, menstrual disorder, prevalence, work disturbance

Abstrak

***Tujuan**: Untuk mengetahui hubungan antara gangguan menstruasi termasuk setiap gangguan siklus menstruasi, durasi dan volume gangguan perdarahan menstruasi, gangguan interval menstruasi, dan kelainan lain yang berhubungan dengan menstruasi terhadap terganggunya kerja pada karyawan.*

***Metode**: Penelitian ini menggunakan desain potong lintang dengan jumlah sampel sebanyak 150 responden. Pengacakan sampel dengan perangkat lunak winpepi® untuk Windows 7®. Analisis data menggunakan software SPSS 24® untuk Wndows 7®.*

***Hasil**: Prevalensi gangguan menstruasi adalah 87%, gangguan siklus haid 3%. Gangguan volume menstruasi 31%, kelainan menstruasi 15%, 83% gangguan nyeri haid dan sindrom pramenstruasi 71%. Prevalensi 49% gangguan kerja ringan, gangguan kerja sedang 47% dan gangguan kerja berat sebesar 4%. Adanya hubungan antara gangguan volume menstruasi, hipermenorea, dan nyeri haid / dismenore terhadap gangguan kerja di antara karyawan di RSCM (p <0,001). Pengajuan hari cuti yang diusulkan karena gangguan menstruasi terbanyak adalah 1 hari yaitu sebesar 73%.*

***Kesimpulan**: Prevalensi gangguan berat pekerjaan akibat haid tidaklah tinggi namun bisa mengakibatkan terganggunya pekerjaan dan aktivitas yang berjalan, namun, penting untuk menjadi perhatian agar karyawan mendapatkan manajemen dan perawatan yang baik.*

[Maj Obstet Ginekol Indones 2018; 6-1: 10-17]

***Kata kunci**: cuti haid, gangguan haid, gangguan kerja, karyawan, prevalensi*

INTRODUCTION

Menstruation is a God-given nature to women. Menstruation is like a close friend who is present to accompany a woman every month. However, sometimes menstruation can be unpleasant and may lead to problems named as menstrual disorders. According to the World Health Organization (WHO), approximately about 18 million women aged 30-55 years experienced menstrual disorders in the form of excessive menstrual blood.[1] In the work environment, the majority hospital workers are dominated by women workers, particularly those who work as nurses.[2] In the female worker's group, menstrual disorders, including premenstrual syndrome, menstrual pain disorder (dysmenorrhoea), long disturbance and amount of bleeding, and menstrual cycle disorders, often occur.[3]

Menstrual disorders among female workers cannot be disregarded. Dysmenorrhoea, long disturbances, as well as long and excessive menstrual periods (hypermenorrhoea), may affect

women's quality of life and economically lead to reduced income due to lost working time and work productivity of the women workers for 2-3 days in each month.[1,4] In fact, because of their business or perhaps due to the lack of awareness and limited understanding of menstrual disorders, they sometimes have less chance to find the cause of the menstrual disorder. If the menstrual disorder an excessive amount of bleeding caused by involves endometrial hyperplasia, it usually occurs at the age of menopause but also by 25% of cases can occur at perimenopausal age and by 5% at age less than 40 years.[5,6] If the type of hyperplasia is included Atypical groups will increase the risk of endometrial cancer by 8% in type Simple Atypical Hyperplasia (SAH) and 29% in Complex Atypical Hyperplasia (CAH) if the endometrial hyperplasia is not treated promptly.[7] Complaints of menstrual disorders can also occur in cervical cancer in women aged 25-65 years.[8]

Studies regarding menstrual disorders among adolescents, women workers, and nurses abroad have been done.[2,3,9] Among them through study results Nohara, et al mentions the prevalence of menstrual pain disorder (dysmenorrhea) and menstrual cycle disorders among office workers in Japan is quite high Namely by 76.5% and 17.1%. Meanwhile, according to Smith, et al. mentioned that the prevalence rate of menstrual cycle disturbances, other menstrual disorders in this case in the form of menstrual pain (dysmenorrhea), and premenstrual syndrome, among nurses in Japan, were 24.9%, 44.6%, and 42.2%. Nohara et al. found that there was a possibility of linkage to the increase of menstrual cycle disorders and menstrual pain disorder in the employee who experiencing stress.[2,3] Then how about the similar study in Indonesia, it turns out the study on new menstrual disorders reside in student or the adolescent environment.[10] However, the study on menstrual disorders among employee working in hospital environments in Indonesia is still very limited.

On the other hand, the Government of Indonesia has actually shown its care through the Law of the Republic of Indonesia number 13, 2013 on Employment in article 81 on the permissibility of taking menstrual leave due to menstrual pain experienced by a woman worker for 2 days on the first day and second at the time of menstruation.[11,12] The law was established with the aim to protect women workers in Indonesia. Both formal and informal sectors that experience problems of menstrual disorders especially pain during menstruation. The purpose of the policy is actually expected that women workers who experience menstrual disorders can use this time to examine himself to the expert doctor about the disorder are to find the cause and treat menstrual disorders are. In fact, similar policies have not yet existed in the working environment of Government Hospital. The absence of such policy could be due to the absence of such menstrual leave policy, due to the absence of any obvious problems regarding menstrual disorders, so that the policy is difficult to consider. So to answer the above, this study is done with the aim to know the characteristics of menstruation and prevalence of menstrual disorder that happened to the worker who works in a hospital environment, and this study also conducted as one of the means to increase awareness and knowledge from the women about their menstrual disorders. The results of this study can also be used as a basis to determine whether or not the existence of a new policy regarding the giving of leave time on the employee who experienced menstrual disorders in terms of how big the problem occurred.

METHODS

This was a cross-sectional study. The survey was conducted at Dr. Cipto Mangunkusumo National General Hospital (RSUPNCM) Jakarta. Study and sampling using questionnaires and diary forms of menstrual disorders began in January 2017 until April 2017. Inclusion criteria were RSCM employees who were willing to follow the study, employee aged 20-50 years. The lowest age is the average age of women employed in RSCM, while the upper age is used based on the 2004 PERMI survey of the average age of menopause in Indonesia.[13] The exclusion criteria in this study were those who were pregnant and not experiencing pregnancy within 3 months. Prior to informed consent, and respondents have experienced menopause. Based on the calculation of the number of respondents, then the respondent's minimum in this study the researchers chose the results of large sample calculations based on the proportion of respondents in the largest case of menstrual pain (dysmenorrhoea) as 138 respondents. Large respondents are

considered capable of management as respondents study in this study. Respondents in this study were part of affordable population selected after selection through inclusion and exclusion criteria, then respondents were randomized using simple random sampling method for the employee who worked at RSCM who was in the workplace when survey by the researchers who then included in the study until the number of respondents desired is met. From employment data as of 31st October 2016, there is a total of 3700 employees of the study process conducted in January 2017 to April 2017. The results of the questionnaires were collected and checked by the respondents within 30 minutes of the questionnaire. All Collected data is recorded and analyzed. A questionnaire was validated by cronbach alpha method using the software program SPSS 24® for Windows 7® program. The questionnaire has been validated to 20 employees using winpepi® software for Windows 7® and obtained by alpha cronbach value of 0.8 with good internal consistency criteria.

All statistical analyses were performed using SPSS 24 for Windows. Results were displayed in the form of frequency, percentage (proportion), the average (mean), median, range values (range). Normality test data distribution to the numerical data that is Kolmogorov-Smirnov and Shapiro-Wilk test the hypothesis is done by using analytic comparative categorical unpaired such as Chi-square and alternatives that Kolmogorov-Smirnov when not qualify Chi-square test and test analytic comparative numerically paired unpaired t test when data distribution was normal and alternatives such as the Mann-Whitney test if data distribution is not normal that is used to verify a possible correlation between the variables. All hypothesis test analysis results are shown with significance level p <0.05.

RESULTS

The number of study subjects that can be collected as many as 150 people, obtained from the employee working at RSCM in Building A, Kirana and Kiara RSCM in the period November of 2016 until April 2017.

Table 1. Subject Characteristics

Variable	Number of subject (%), N=150
Age group (years)	
<25	33 (22)
25-29	40 (27)
30-34	19 (13)
35-39	31 (21)
40-44	15 (10)
45-49	10 (7)
50-54	2 (1)
BMI (kg/m²)	
<18.5	8 (5)
18.5-25.0	98 (65)
≥ 25.0	31 (21)
>30	13 (9)
Education	
Senior High School	7 (5)
D3	108 (72)
D4	4 (2)
S1	31 (21)
Marital Status	
Married	101 (67)
Not yet married	49 (33)
Number of Pregnancy	
0	63 (42)
≥ 1	87 (58)
Number of Labor	
0	64 (42.7)
≥ 1	86 (57.3)
Number of Misscariage	
Never	128 (85)
≥ 1 times	22 (15)
Work status	
Permanent worker	127 (85)
Unfixed worker	23 (15)
Shift work	
Morning Shift	145 (96.7)
Afternoon Shift	116 (77.3)
Night Shift	113 (75.)
One-Shift	31 (21)
Two-Shift	5 (3)
All shift	114 (76)

Work hours	
< 7 hours/day	3 (2)
8-10 hours/day	139 (93)
> 10 hours/day	8 (5)
Position on work	
Sitting	17 (11)
Standing/walking	18 (12)
Both	115 (77)
Sleep duration	
< 6 hours	59 (39)
> 6 hours	91 (61)
Smoking habits	
Active smoker	0 (0)
Pasive smoker	0 (0)
Non smoker	150 (100)
Exercise	
Yes	1 (1)
Not	149 (99)
Age of menarche	
9	0 (0)
10	2 (1)
11	10 (7)
12	51 (34)
> 12	87 (58)
Menstrual duration	
< 3 days	0 (0)
3-7 days	125 (83)
> 7 days	25 (17)
Contraception	
Natural contraception	2 (1)
Condom	7 (5)
Amenorea Lactation methods	0 (0)
COC	4 (3)
Minipil	0 (0)
1 month injection contraception	0 (0)
3 month injection contraception	4 (3)
Implant	0 (0)
IUD	27 (18)
Tubectomy	2 (1)
Not used	104 (69)

From the result above, the highest employee age range is aged 25-29 years by 40 employee (27%). The mean value of the worker's age is 31.8 years with a standard deviation value of 7.9 years. The age of the youngest employee respondents is 21 years old with the age of the oldest employee respondents is 52 years old. From this result it can be seen that the average of worker's age is slightly younger than the result of the study on the previous employee in Japan.[2]

About 65% of employees at RSCM have average BMI of Normal Weight (Normoweight) category which is 23.9 kg / m^2 almost similar to employee in Japan, USA and Norway.[2,4,14] The employees at RSCM are dominated by D3 level of education as much as 108 (72%). The second is S1 (31%), high school education (7%) and 4 (3%) of D4 education.

From the above study shows that the majority of workers as many as 101 people (67%) employees had been married and 49 people (33%) unmarried employee. In contrast to previous study results that the majority was dominated by unmarried workers.[2]

Majority of the workers were married and have had 87 pregnant women (58%). Employees who have never had a pregnancy are 63 (42%) but only 14 (9%) are actually married but have never been pregnant and 49 (%) are unmarried. And have never been pregnant. With a mean value of 1.82 pregnancies with standard deviation of 1.3 pregnancies. With a median of 2 pregnancies.

A total of 86 workers (57.3%) who were married experienced pregnancy, and later there were 14 people (9.3%) who were married but had never been pregnant or had labor and had experienced labor and there were only 1 (0.7%) employed married then pregnant but had never experienced labor because of miscarriage. As many as 57.3% of workers in this study had experienced labor. The average number of deliveries was 1.61 births with standard deviation of 1.04 births. With a median value of 2 deliveries. Compared to previous study, the number of marriages among RSCM employees was quite high, similar to that of Gordley et al. study, among 56% of female workers in the United States, 56.3% had been married and 58.3% have children. Then for pregnancy and delivery rates in this study was higher than in Japan according to Nohara et al. were as much as 40.5% had experienced pregnancy and as much as 38.4% had experienced labor. Thus the nulliparous rate in this study was less than the results of study on the previous employee in Japan that was equal to 60.4% of

employees have not had children.[3,4]

From the table above shows that there are 22 people worker (15%) have experienced miscarriage. As many as 128 employees (85%) had never experienced a miscarriage. With a mean value of 1.03 miscarriage and a standard deviation value of 0.86 miscarriage. Then obtained the median value of 1 miscarriage. Employment status is dominated by permanent workers, ie 127 workers (85%). And workers are not fixed as many as 23 employee (15%).

From the division of working time there are 93 employees (38%) who work on 3 shifts division of working time in the morning, afternoon and night shift.

Based on working hours, 139 workers (93%) worked for 8-10 hours per day. A total of 8 employees (5%) work more than 10 hours per day and as many as 3 employees (3%) work less than 7 hours per day. With the average value of working for 8.3 hours with a standard deviation value of 1 hour. With a median value of 8 hours. The length of working hours is almost similar to the length of working hours employed based on previous study in Japan with a mean value of 8.9 hours and standard deviation 1 hour.[2]

Based on the position at work obtained results that as many as 11 employees (45%) work in 3 positions of sitting, standing and walking. Then based on long hours of sleep there are 91 people (61%) with long hours of sleep more than 6 hours per day. While on the worker with long hours of sleep less equal to 6 hours per day was as many as 59 people (39%).

From the table shows there are 150 respondents (100%) had never smoked. And there were 149 employees (99%) who did not exercise regularly and 1 person (1%) was used to regular exercise.

Based on the age of menarche, it was found that most of the employees had menarche age more than 12 years (58%). Age 12 years of 51 (34%). Age 11 years as many as 10 people employee (7%). Age 10 years as many as 2 employee (1%). With a mean value of 13 years with standard deviation of 1.3 years, and median value at age 13 years.

Based on the duration of menstruation there are 125 people (83%) with menstrual period 3-7 days. Then as many as 25 employee (17%) with menstrual period of more than 7 days. The mean value was 6.6 days and the standard deviation value was 1.65 days. With median duration of menstruation was 7 days.

Table 2. Correlation between Menstrual Disorder and Work Disturbance

		Work disturbance						*X2	*p	**Asymp. Sig (2-tailed)
		mild		moderate		severe				
		n	%	n	%	n	%			
Menstrual disorder	Not disturbed	17	11.3	2	1.3	0	0	14.065	0.001	-
	Disturbed	57	38	68	45.3	6	4			
Menstrual cycle disorder	Not disturbed	71	95.9	69	98.6	6	100	1.127	0.569	0.949
	Disturbed	3	4.1	1	1.4	0	0			
Menstrual volume disorder	Not disturbed	63	42	39	26	2	1.3	18.454	0.000	0.000
	Disturbed	11	7.3	31	20.7	4	2.7			
Menstrual periode disorder	Not disturbed	66	44	58	38.7	4	2.7	2.892	0.235	-
	Disturbed	8	5.3	12	8	2	1.3			
Hypermenorea	Not disturbed	59	39.3	36	24	2	1.3	15.295	0.000	0.001
	Disturbed	15	10	34	22.7	4	2.7			
Dismenorea	Not disturbed	23	15.3	3	2	0	0	19.5	0.000	0.000
	Disturbed	51	34	67	44.7	6	4			
Premenstrual syndrome	Not disturbed	22	14.7	19	12.7	1	0.7	0.518	0.772	1.000
	Disturbed	52	34.7	51	34	5	3.3			
		74	100	70	100	6	100			

Table 3. Correlation between Level of Pain with VAS Score, PBAC Score and Work Disturbance

VAS Score					
		n	**Median (Minimum-Maximum)**	**Mean ± SD**	**p**
Work disturbance	Mild	74	2 (0-6)	1.77 ± 1.46	< 0.001
	Moderate	70	4 (0-8)	3.74 ± 1.66	
	Severe	6	8 (6-8)	0.168 ± 0.84	
PBAC score					
Work disturbance	Mild	74	74.5 (4-180)	74.9 ± 36.0	< 0.005
	Moderate	70	96 (10-456)	113.9 ± 86.5	
	Severe	6	132 (81-170)	130 ± 35.8	

VAS score vs work disturbance : Kruskall-wallis test. Post hoc Mann-Whitney test: severe vs moderate p < 0.001; Severe vs mild p < 0.001; moderate vs mild p <0.001
PBAC score vs work disturbance : Kruskall-wallis test. Post hoc Mann-Whitney test :severe vs moderate p < 0.135; severe vs mild p = 0.003; moderate vs mild p = 0.001

Of the 101 married workers, 46 (45.5%) married workers used contraceptive methods while 55 (54.5%) did not use any method of contraception. The highest type of contraception methods was IUD with 27 (26.7%) subjects.

Based on the distribution of respondents who experienced menstrual disorders were 131 employees (87.3%) and 19 employees (12.6%) did not experience menstrual disorders.

Based on the proportion of the distribution of respondents by type of menstrual disorders that most are in other disorders associated with menstruation as many as 130 people (87%), followed by disruption volume of menstrual many as 46 people (31%), disruption of menstrual periode as many as 22 people (14.6%), and disruption of other menstrual bleeding outside the menstrual cycle 4 people (3%). This result is in accordance with previous studies.[2-4]

DISCUSSION

In this study, the most menstrual cycle disorder type was the case of polymenorrhea as much as 3 subjects (2%) and oligomenorrhea as much (1%). In other studies, according to Smith et al. mention that menstrual cycle disorder is as much as 24.9%, then according to Nohara et al. is 17.1%. According to Gordley et al. said menstrual pain among military personnel in the United States is 12%. Meanwhile, according to Moen et al. for menstrual cycle disorders at an employee in Norway amounted to 19% with polimenorea 17% and oligomenorrhea of 2%.[2-4,14]

Then the type of highest menstrual periode and the menstrual volume disorders is hypermenorea (Menorragia / Heavy Menstrual Bleeding / HMB) as many as 53 people (35%). According Gordley et al. said for a menstrual periode and menstrual volume disorders amounted to 17.9%, while according to Moen et al. study just mentioned about the menstrual periode disorders that is equal to 20% and 19% for Hipomenorea.[4,14]

While in the assessment of bleeding disorders outside the menstrual cycle results obtained no employee bleeding disorders outside the menstrual cycle (metroragia / intermenstrual bleeding). Lack of study exists on the results of menstrual cycle disorders and bleeding disorders outside the menstrual cycle which comparatively few because making questionnaire answers by using diaries menstruation is only done on the observation of menstruation within 1 month prior to filling the questionnaire which should be monitoring menstrual cycle disorders should be at least in the next 3 months after filling the questionnaire, but also due to the limited time of study from the researcher while the respondents of the study mostly only able to remember and record of when the menstruation of each respondent is not good, causing the least number of menstrual cycle disorders.

In this study, we found that, based on other disorders associated with menstruation, it was found that were dysmenorrhea 124 (83%) and premenstrual syndrome were 107 (71%). This is in accordance with previous study, Nohara et al. in Japan, the prevalence rate of menstrual pain

disorder (dysmenorrhea) among office workers in Japan is quite high at 76.5%. Meanwhile, Smith et al. found that menstrual pain (dysmenorrhoea) among nurses in Japan was 90.1% which was divided into the pain is occasionally felt by 45.5% and pain was always felt by 44.6%, while for premenstrual syndrome 88.7% divided into occasionally premenstrual syndrome 42.2% and always feel premenstrual syndrome equal to 46.5%. While Gordley et al. said menstrual pain among military personnel in the United States amounted to 31.2%, the study found that most complaints in employee complaints is in the form of painful menstruation or dysmenorrhea and premenstrual syndrome.[2-4]

Based on the degree of menstrual pain using VAS score, it was found that most complaints were mild pain complaints of 65%, followed by moderate pain complaints of 29%, and then 6% of employee complained of severe pain.

Based on the location of pain relief most painful menstruation is felt to spread to the lower abdomen as much as 56%, pain 22% waist, stomach pain that spread to the thigh as much as 5% and pain relief to other places such as thighs and anus as much as 3%, while as many as 14% the employee said there were no pain complaints.

Based on the types of complaints related to menstruation, it is found that most mental complaints are in the form of irritability and irritability by 31%, followed by easy complaints of weakness, fatigue and lethargy and tiredness as much as 21%, mood changes that arrived (feelings of sudden sadness) as much as 18%, appetite increased by 8.7%, anxiety and tension feeling as much as 3.8%, feelings of sadness and no hope as much as 3.5%, easy to fall asleep and difficulty awakened or lack of sleeplessness as much as 2.1%, while as many as 8.7% employee admitted no complaints to the mental. While in the study of Smith et al. there are few differences where it is mentioned that most mental complaints are in the form of weakness, fatigue and lethargy and fatigue of 23.4%, excessive hunger by 11.5%, difficulty sleeping by 3%, anxious excess of 2.9%, decreased appetite 2.4%.

Based on the physical complaints obtained results that most complaints are in the form of pain complaints in the breast as much as 32%, followed by breast swelling of 19%, abdominal bloating 16%, 14% headache, swelling in the arm or leg as much as 1%, pain in the buttocks 1%, body poppy 0.5% and acne 0.5%. According to Smith's et al. study there are 4 most physical complaints from the Japanese workers, namely 49.2% breast pain especially felt before the menstrual period. Then 47.3% of stomach pain was felt before menstruation and increased during menstruation lasting that is equal to 76.2%, 42.6% of waist pain felt higher when menstruation equal to 64%, and headache felt at 24.3% and decreased during menstruation took place in as many as 22.9% of employees in Japan.[2]

Later in this study obtained the results of the most impact of menstrual disorders on the work was a mild impact and does not interfere with activity and work by 49% and not much different from the impact of interference while there are 47% feel the impact of menstrual disorders, where the employees can still continued work despite being disturbed. Severe disturbance is felt in 4% of employees.

From this study it is known that the relationship between menstrual volume disorder, hypermenorrhea, and menstrual pain / dysmenorrhoea have a relationship with work disruption at the employee at RSCM with ($p < 0.001$). While the menstrual cycle and the menstrual periode disorder and premenstrual syndrome have no relation to work disruption at employee at RSCM (Table 2).

VAS score with moderate and severe pain has correlated with work disturbance ($p<0.001$) and PBAC score with moderate and severe has correlated with work disturbance ($p<0.005$) (Table 3).

Based on the permit break due to work disruption where there was 16% using a permit to rest due to menstrual disorders. The length of permit taken is 20.7% taking 1 day leave and as much as 0.7% taking the menstrual leave for 2 days. But mostly 78.7% of the employee did not take time off.

Most of the workers did not know about menstruation leave policy where only 15% of employee who know of menstrual leave policy, most policies are made in private hospitals, and as many as 85% of workers mention not knowing the existence of menstruation leave.

The proposed leave of absence from menstrual abnormalities in the proposed permit for 1 day (73%), then as many as 18% apply for leave for

2 days, while as many as 15% said not require menstruation leave.

CONCLUSION

The prevalence of severe labor disruption due to menstruation is not high but can lead to disruption in running jobs and activities. However, it is important to be a concern so that the employees get right management and care. Menstrual volume disorders, hypermenorrhoea, and menstrual pain/ dysmenorrhoea have a significant relationship with work disturbance at the RSCM employee. While the menstrual cycle disturbances, menstrual periode disturbances and premenstrual syndrome have no relation to work disturbance at employee at RSCM.

REFERENCES

1. Karout N, Hawai SM, Altuwaijri S. Prevalence and pattern of menstrual disorders among Lebanese nursing student. East Mediterr Health J. 2012; 18(4): 346-452.
2. Smith DR, Mihashi M, Adachi Y, Shouyama Y, Mouri F, Ishibashi N, et al. Menstrual disorders and their influence on low back pain among Japanese nurses. Ind Health. 2009; 47(3): 301-12.
3. Nohara M, Momoeda M, Kubota T, Nakabayashi M. Menstrual cycle and menstrual pain problems and related risk factors among Japanese female workers. Ind Health. 2011; 49(2): 228-34.
4. Gordley LB, Lemasters G, Simpson SR, Yiin JH. Menstrual disorders and occupational, stress, and racial factors among military personnel. J Occup Environ Med. 2000; 42(9): 871-81.
5. Plataniotis G, Castiglione M. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010; 21 (Supp 5): 41- 5.
6. The University of Texas MD Anderson Cancer Center. Patient and Cancer Information: Uterine Cancer. 2013 [cited 2013 June 2]. Available from: http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-types/uterine-cancer/index.html.
7. Endometrial (Uterine) Cancer 2013 [cited 2013 May 31]. Available from: http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-uterine-cancer-risk-factors.
8. Cancer Study UK. Cervical cancer incidence statistics. 2013 [cited 2013 June 2]. Available from: http://www.cancerstudyuk.org/cancer-info/cancerstats/types/cervix/incidence/uk-cervical-cancer-incidence-statistics.
9. Fujiwara T, Nakata R. Young Japanese college students with dysmenorrhea have high frequency of irregular menstruation and premenstrual symptoms. Open Med Inform J. 2007; 1: 8-11.
10. Sianipar O, Bunawan NC, Almazini P, Calista N, Wulandari P, Rovenska N, et al. Prevalensi Gangguan Haid dan Faktor-faktor yang berhubungan pada Siswi SMU di Kecamatan Pulogadung Jakarta Timur. Maj Kedok Indones. 2009; 59(7): 308-13.
11. Undang-Undang Republik Indonesia No. 13 Tahun 2003 Tentang Ketenagakerjaan, pasal 81.
12. Rizky MA, Haryanto ND. Perlindungan Hukum Terhadap Tenaga Kerja Perempuan dan Hambatan-Hambatan yang Dihadapi. Fakultas Hukum Universitas Sebelas Maret. 2016
13. UPI WF. Menopause Berseri dengan Drosperinone dan Estradiol[cited 2013 June 19]. Available from: www.forum.upi.edu/index.php?topic=13107.0.
14. Moen BE, Baste V, Morken T, Alsaker K, Pallesen S, Bjorvatn B. Menstrual characteristics and night work among nurses. Ind Health [Internet]. 2015; 53(4): 354-60.

Research Article

The Association of C-Reactive Protein Levels in Second Trimester of Pregnancy with Preeclampsia

Hubungan Kadar C-Reactive Protein pada Kehamilan Trimester II dengan Preeklamsia

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Abstract

Objective: To determine C-reactive protein in second trimester of pregnancy women who preeclamptic and non-preeclamptic women, and to determine the relationship between the level of C-Reactive protein of trimester two pregnancy and preeclampsia occurrence.

Methods: This was a prospective study conducted at the policlinics of network of academic hospitals of the Department of Obstetrics and Gynecology of Faculty of Medicine, Universitas Hasanuddin and policlinic of child and mother, and some Public Health Centers in Makassar city from September 2015 - April 2016. The C-reactive protein 115 level of pregnant women in pregnancy age of 24-28 weeks was checked, whether the subjects underwent preeclampsia until the childbirth process. Statistics analysis used Fisher's exact test and Mann Whitney test.

Results: The result indicate that 9 subjects (7.8%) developed preeclampsia and 106 subjects did not become preeclampsia. The level of C-Reactive protein increased in preeclampsia group compared to non preeclampsia group i.e 5.05 ± 1.153 : 3.36 ± 0.265, but statistically the result is not significant (value p>0.05).

Conclusion: The average score of C-Reactive protein of preeclampsia group is 33.5% higher than non-preeclampsia group, even though these results cannot be used as the score to predict the preeclampsia occurrence.

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Keywords: C-reactive protein, preeclampsia, second trimester pregnancy

Abstrak

***Tujuan**: Mengetahui kadar C-Reactive Protein perempuan hamil trimester dua yang menjadi preeklamsia dan bukan preeklamsia, serta mengetahui hubungan antara kadar C-Reactive Protein kehamilan trimester dua dengan kejadian preeklamsia.*

***Metode**: Penelitian ini menggunakan rancangan kohort prospektif, dilaksanakan di Poliklinik RS jejaring pendidikan Departemen Obstetri dan Ginekologi FK UNHAS dan Poliklinik Kesehatan Ibu dan Anak dan beberapa Puskesmas Kota Makassar selama September 2015 - April 2016. Dilakukan pemeriksaan kadar C-Reactive Protein 115 ibu hamil pada usia kehamilan 24 - 28 minggu, kemudian diamati apakah subjek mengalami preeklamsia hingga proses persalinan. Analisis statistik menggunakan uji Fisher's exact dan uji Mann Whitney.*

***Hasil**: Didapatkan hasil 9 subjek (7,8%) berkembang menjadi preeklamsia dan 106 subjek tidak menjadi preeklamsia. Terjadi peningkatan kadar C-Reactive Protein pada kelompok preeklamsia dibanding kelompok bukan preeklamsia yaitu 5,05 ± 1,153 : 3,36 ± 0,265 tapi hasilnya tidak bermakna secara statistik (nilai p>0,05).*

***Kesimpulan**: Nilai rerata kadar C-Reactive Protein kelompok preeklamsia 33,5% lebih tinggi dibandingkan dengan kelompok bukan preeklamsia, namun hasil ini belum dapat digunakan sebagai nilai untuk memprediksi kejadian preeklamsia.*

[Maj Obstet Ginekol Indones 2018; 6-1: 18-22]

***Kata kunci**: C-Reactive Protein, kehamilan trimester dua, preeklamsia*

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INTRODUCTION

The three major causes of maternal mortality in Indonesia are bleeding (30%), eclampsia (25%) and infection (12%). The World Health Organization (WHO) estimated that the rate of preeclampsia were seven times higher in developing countries compared to developed countries. The prevalence of preeclampsia in developed countries ranges from 1.3% to 6%, while in developing countries from 1.8% to 18%. The incidence of preeclampsia in Indonesia is 128 273 per year, or 5.3%.[1]

During the last 8 years (from 2005 to 2013), the incidence of severe preeclampsia tends to increase at Dr. Wahidin Sudirohusodo Hospital. The incidence of severe preeclampsia in 2005-2007 by 8%, rising to 8.6% in the period 2007-2009, then in 2009-2011 increased by 13.47% and in the period of 2011-2013 the incidence up to 16.51%.[2]

Preeclampsia is best described as a special-pregnancy syndrome involving multiorgan systems.[3,4] In the past, preeclampsia could be diagnosed whenever we found its clinical triad i.e,

blood pressure ≥ 140/90 mmHg, proteinuria and edema. Currently, edema is no longer be included in the diagnostic criteria for preeclampsia because edema was also observed in normal pregnancy. Proteinuria was defined as urinary protein excretion exceeds 300 mg in 24 hours, the ratio of protein: urinary creatinine ≥ 0.3 or presence of protein as much as 30 mg / dl (1+) in a random sample of urine is settled.[1,5]

The risk factors that have been identified can be helpful in assessing the risk of pregnancy in early antenatal visit. There are two parts of risk factors of preeclampsia, included high risk factors (major factors) and additional (minor factors). High risk for preeclampsia is history of preeclampsia in a previous pregnancy, multiple pregnancy, diseases that accompany pregnancy (chronic hypertension, diabetes mellitus, chronic kidney disease and phospholipid syndrome). Additional risk factors are the body mass index ≥ 35 kg/m^2, vascular diseases, maternal age ≥ 40, nullipara (the first pregnancy with a new partner or a previous pregnancy is ≥ 10 years), a history of preeclampsia at her mother or sister, pregnancy with donor sperm insemination, oocyte or embryo, diastolic blood pressure ≥ 80 mmHg, and proteinuria.[1]

A study conducted by Rozikhan, in Kendal Hospital found that the risk factors of severe preeclampsia were significantly in the presence of history of preeclampsia (p = 0.001), descent (p = 0.001), the first child parity/ nullipara (p = 0.001).[6]

To this date, there are various findings of biomarkers that can be used to predict the incidence of preeclampsia, but none of these tests that have high sensitivity and specificity as well as there is no test filters that are reliable, valid and economical.[3]

C-Reactive Protein (CRP), a sensitive marker for inflammation and tissue damage, can be a potential marker. Plasma level of CRP increases in cases of acute infection, malignancy, and inflammatory diseases. CRP can bind to chromatin, which is released from necrotic cells or apoptotic cells, and to a small ribonucleoprotein nucleus particles. This shows us that the CRP, in the adjustment function, can play a role in inducing the inflammatory response that is characteristic of preeclampsia.[7] Based on that study, our study want assessed the relationship levels of C-Reactive Protein in the second trimester of pregnancy with preeclampsia.

METHODS

This study was conducted at the networking of Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Hasanuddin and primary health centers in the city of Makassar. This study was designed as a prospective cohort study. Consecutive sampling by the number of subjects 115 people. Subjects who suited for the criteria sample of pregnant women at trimester II, then were informed about how's the purpose and objective of the study is worked, and who are willing to participate the study will sign a consent form and then examination was performed. After that we do the questionnaires, included the form data of anamnesis, physical examination and laboratory investigation. Blood samples were taken as much as 3 cc by using a tube serum separator tube (SST) and then they will be sent to a laboratory for examination (Prodia Makassar Laboratory) for measure the levels of C-reactive protein. Patients were followed monthly their pregnancy until the labor time. Final data capture and collect include preeclampsia and time of birth. Data analysis using Fisher's Exact test and Mann Whitney test.

The inclusion criteria of this study were pregnant women with second trimester of pregnancy (24-28 weeks) that antenatal and planned deliveries in the city of Makassar, and women with a complete personal identity and has a phone number that can be contacted and volunteered to followed this study.

Pregnant women with history of metabolic diseases such as diabetes mellitus, cardiovascular disease, and coronary heart disease, were excluded. And if the blood sample lysis, the data were incomplete or did not follow the entire procedure, and patients withdrew for certain reasons.

RESULTS

In this study, we got 115 of the second trimester pregnant women, with gestational age range 24-28 weeks who were willing to be the subject of study from the beginning to the end of the study. Of the 115 subjects, obtained 9 (7.8%) of women who become preeclampsia during the study and serve as a research group, and 106 people who did not become preeclampsia used as a control group. From Table 1 we can see the tendency of

preeclampsia occurs at age 20-35 years, women who did not work, and multiparous.

Table 1. Distribution of General Characteristic of the Samples

Characteristic	Preeclampsia (n = 9)		not Preeclampsia (n = 106)		p
	n	%	n	%	
Age (years)					
< 20 and > 35	2	22.2	28	26.4	0.569
20 - 35	7	77.8	78	73.6	
Occupation					
Employer	3	33.3	15	14.1	0.147
Housewife	6	66.7	91	85.9	
Parity					
Nullipara/ primipara	4	44.4	74	69.8	0.118
Multipara	5	55.6	32	30.2	

In Table 2, the data stratified by risk factors of preeclampsia. Of the 23 subjects who did not have the risk factors were 2 (8.7%) subjects who developed into preeclampsia, whereas 92 subjects with risk factors obtained 7 subjects who developed into preeclampsia. Between 5 of preeclampsia risk factors identified in the study subjects, subjects with risk factors of age over 40 years (16.7%), Nulli / primiparous (5.1%), history of previous preeclampsia (33.3%), a history of hypertension in pregnancy in mothers or sisters (10%), which later developed into preeclampsia, although not statistically significant (p <0.05).

Table 3 shows the mean value (mean) of C-Reactive Protein in the preeclampsia group and non-preeclampsia group. There is no significant found a relationship between preeclampsia group and non-preeclampsia group instead in case of elevated levels of C-Reactive Protein.

Table 3. Correlation between C-Reactive Protein with Preeclampsia

	Preeclampsia (n = 9)	No Preeclampsia (n = 106)	p
CRP level	5.05 ± 1.153	3.36 ± 0.265	0.094

In addition, the mean CRP levels in those with preeclampsia was 33.5%, higher when compared with the group with not preeclampsia. Figure 1 shows the distribution of CRP levels in the study subjects. Figure 2 shows the difference in CRP between groups of preeclampsia and non-preeclampsia. In the plot of these data, it appears that CRP levels are not evenly distributed well. It looks at the median value which is not precisely in the middle of the box and whisker at the top and bottom do not have the same length, one of another has a length more than others. It can be concluded that CRP levels are not distributed normally.

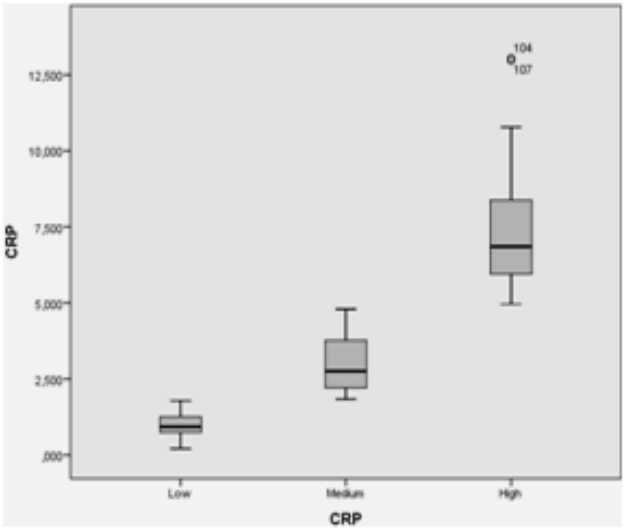

Figure 1. Spreading of C-Reactive Protein Level at Various Samples Study

Table 2. Characteristic Datas of the Risk Factors of Preeclampsia

Characteristic	Preeclampsia		no Preeclampsia		Total	p
	n	%	n	%		
No risk factor	2	8.7	21	91.3	23	0.572
Age > 40 y.o	1	16.7	5	83.3	6	0.394
Nulli/Primipara	4	5.1	74	94.9	78	0.118
History of prior preeclampsia	1	33.3	2	66.7	3	0.219
History of hypertension in pregnancy at their mothers or sisters	1	10	9	90	10	0.573
Gemelli delivery	0	0.0	2	100	2	0.849

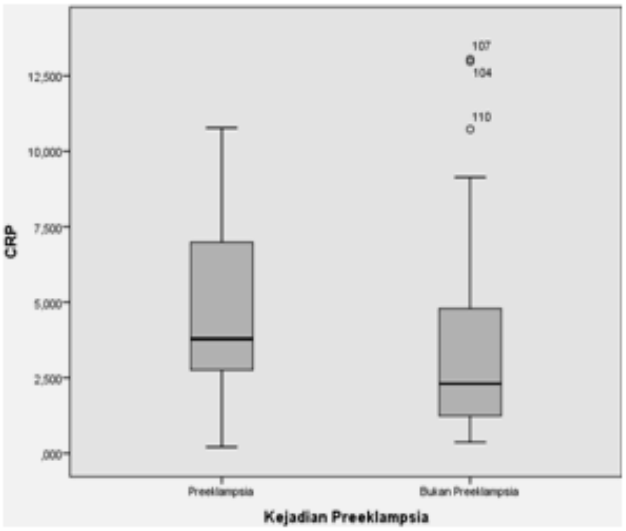

Figure 2. The Difference between CRP Level of Pre-eclampsia Group and non-Preeclampsia Group

DISCUSSION

The results of this study showed that 115 samples with second trimester of pregnancy whose CRP levels were checked, as much as 9 subjects who develop preeclampsia. Of the 9 patients who develop preeclampsia, a total of 4 patients had higher levels of C-reactive protein, which is categorized as high (≥ 4.9 mg / l), 4 patients had medium levels of C-reactive protein, which is categorized as moderate (1.8 - 4.8 mg / l), and there is one patient who had lower levels of C-reactive protein (<1.8 mg / l).

Based on the study results, there is a tendency of patients with preeclampsia had higher levels of C-Reactive Protein. The mean of CRP in patients suffering from preeclampsia is 5.05 mg / l. Of the 9 patients who suffer from preeclampsia, there were two patients who do not have risk factors for preeclampsia. Based on Fisher's Exact test results conducted between risk factors for preeclampsia with the incidence of preeclampsia, there is not found significantly the relationship between risk factors and the incidence of preeclampsia. This means that the risk factors that exist is not a confounding factor in this study.

The incidence of preeclampsia varies; it is affected by parity, race / ethnicity, genetic predisposition, environment, socioeconomy and other factors. It is reported that the incidence of preeclampsia in nulliparous population ranges from 3 to 10%. In this study, we found as many as 23 subjects who did not have preeclampsia risk factors, but there were 2 (8.7%) of them developed into preeclampsia. It shows how a pregnancy can trigger a state of hypertension remains a mystery although more research is trying to solve it.[3]

Extremes of maternal age (under 20 years and above 35 years) increases the risk of pre-eclampsia.[5] In this study, 30 subjects belongs in the extreme age and two of them suffered from preeclampsia. Data on demographic characteristics conducted by Qiu et al (2004) reported that no significant difference between preeclampsia and control groups on the age of the subject.[4] Duckitt and Harrington (2005), report of 5 cohort study of risk factors for preeclampsia, multipara with a history of preeclampsia increases the risk until seven-fold (RR 7.19 95% CI 5.85 to 8.83) on five cohort studies.[8] In this study, we found that between 3 subjects who have risk factors multi-para with a history of preeclampsia earlier, gained 1 (33.3%) subjects experienced preeclampsia. Subjects with a history of preeclampsia in their mother and sister of three-fold increase risk (RR 2.90 95% CI 1.49 to 8.67), and 10 cases obtained 1 (10%) incidence of preeclampsia, although not statistically there is no significance result ($p < 0.05$).[1,8] It is associated with genetic factors, hereditary tendency due to the interaction of hundreds of genes inherited from both father and mother which controls a number of metabolic and enzymatic functions in every organ, clinically manifest in women who develop preeclampsia.[3]

According Gammill et al (2010), the role of CRP is particularly interesting in the case of obesity, because CRP is closely related to BMI and is also directly affected by the endocrine function of adipose tissue.[9] Benyo et al (2001), shows that there is no difference between the expression of pro-inflammatory cytokines in the placenta of women with preeclampsia compared with controls, so we could say that the increase in inflammatory markers in preeclampsia maternal derived from non-placental source.[10] The main CRP is produced by hepatocytes, under the influence of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Both of pro-inflammatory cytokines are produced by adipose tissue. Interestingly, IL-6 and TNF-α also increased in preeclampsia which is clinically manifested.

The association between obesity and preeclamp-sia has been investigated. In a study aiming to

understand how the mechanisms by which obesity predispose to preeclampsia, Bodnar et al (2005), found that increased of inflammation (measured by CRP), with a combination of hypertriglyceridemia, covering about a third of the increase in such risks.[11] Never the less, in this study, BMI measurement in the second trimester of pregnancy can not be used as a source of data that can be associated with CRP because the measurement based on height and weight during pregnancy is also associated with fetal weight, so they were difficult to assess the real IMT, unlike the BMI measurement before pregnancy or early in pregnancy.

It has been proposed that CRP, in accordance with its function, is able to elicite the inflammatory response characteristic of preeclampsia.[12] CRP is increased in those with preeclampsia; however, there is still debate regarding the potential utility of CRP as an early marker for preeclampsia.[13] Wolf et al showed that elevated levels of CRP during the first trimester in women suffering from preeclampsia, where Savvidou et al (2002), showed that CRP levels at the end of the second trimester was not associated with preeclampsia.[14,15]

In this study of 115 subjects showed whom CRP levels were examined in the second trimester of pregnancy, 9 subjects with preeclampsia was 4 of which have high levels of CRP, and there is one that is low CRP levels but experienced preeclampsia. In addition, of the 106 subjects who did not develop preeclampsia, a total of 26 subjects have high levels of CRP but did not develop preeclampsia. This suggests that the increasing of CRP was not significantly different with the incidence of preeclampsia which was obtained p> 0.094.

CONCLUSIONS

In this study, there were 9 cases of preeclampsia among 115 subjects studied, where there is a tendency of increase in the incidence of preeclampsia in pregnant women with risk factors for age over 40 years, nulli / primiparity, previous history of preeclampsia, and family history of hypertensive disorder in pregnancy. CRP levels in the preeclampsia group on average higher than those not preeclampsia, but these results can not be used as value for predicting preeclampsia. Further research needs to be carried out by using other parameters to determine the extent of C-reactive protein is able to identify women at high risk of developing preeclampsia.

REFERENCES

1. Wibowo N, Irwinda R, Gumilar E, Mose J, Rukmono, Kristanto H dkk. Pedoman Nasional Pelayanan Kedokteran "Preeklamsia". Bakti Husada. 2010: 1-20.
2. Maricar R, Lukas E, Chalid M. Evaluasi Kondisi Maternal dan Luaran Perinatal pada Sindrom Hellp dan Preeklamsia Berat. Indonesia, Bagian Obstetri dan Ginekologi Fakultas Kedokteran Universitas Hasanuddin. 2014: 5-6.
3. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Hauth J, Rouse DJ. Hipertensi Dalam Kehamilan. In Rudi S. (Ed.) Obstetri Williams. 23 ed., ECG Med Publisher. 2010; 7(2): 740-66.
4. Qiu C, Sorensen TK, Luthy DA, Williams MA. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. Am J Hypertens. 2004; 17(2): 154-60.
5. Prawirohardjo S. Hipertensi Dalam Kehamilan. Ilmu Kebidanan. 2010; 6(24): 281-301.
6. Rozikhan. Faktor-faktor Risiko Terjadinya Preeklamsia Berat di Rumah Sakit dr. H. Soewondo Kendal. J Ilmiah Univ Diponegoro Semarang. 2007; 10: 4-5.
7. Tjoa ML, van Vugt JM, Go AT, Blankenstein MA, Oudejans CB, van Wijk IJ. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. J Reprod Immunol, 2003; 59(1): 29-37.
8. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. Department of Obstetrics and Gynaecology; John Radcliffe Hospital, Oxford. 2005.
9. Gammill HS, Powers RW, Clifton RG, Dorsten PV, Hauth JC, Klebanoff MA, et al. Does C-Reactive Protein predict recurrent preeclampsia? National Institute of Health Public Access. Hypertens Pregnancy. 2010; 29(4): 399-409.
10. Benyo DF, Smarason A, Redman CW, Sims C, Conrad KP. Expression of inflammatory cytokines in placentas from women with preeclampsia. J Clin Endocrinol Metabol. 2001; 86(6): 2505-12.
11. Bodnar LM, Ness RB, Harger GF, Roberts JM. Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. Am J Epidemiol. 2005; 162(12): 1198-1206.
12. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999; 180: 499-506.
13. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. Int J Gynecol Obstet. 2001; 75: 243-9.
14. Wolf M, Kettyle E, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol. 2001; 98: 757-62.
15. Savvidou MD, Lees CC, Parra M, Hingorani AD, Nicolaides KH. Levels of C-reactive protein in pregnant women who subsequently develop pre-eclampsia. BJOG: 2002; 109(3): 297-301.

Research Article

Relationship between Vaginal Sialidase Levels with Threatened of Preterm Labour

Hubungan antara Kadar Sialidase Vagina dengan Ancaman Persalinan Prematur

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Abstract

Objective: To investigate the association between vaginal sialidase levels and threatened of preterm labor.

Methods: A cross sectional study design was used. Subjects were divided into two groups; the first group were pregnant women with threatened of preterm labour, whereas the second were preterm pregnant women in Prof. Dr. R.D. Kandou Manado hospitals and network hospitals, during the period between August 2016 and October 2016. Data were analyzed with SPSS version 20 to see the significancy levels.

Results: From the 16 pregnant women with threatened of preterm labor and 16 pregnant women with preterm pregnant, the statistical t test showed that there were significant differences average level of sialidase vagina between the threatened of preterm labor and preterm pregnant group (p = 0.000).

Conclusion: There is a relationship between the incidence threatened of preterm labor with vaginal sialidase levels.

[Indones J Obstet Gynecol 2018; 6-1: 23-27]

Keywords: bacteria, threat of preterm labour, vaginal sialidase

Abstrak

***Tujuan**: Untuk melihat adanya hubungan antara kadar sialidase vagina dengan ancaman persalinan prematur.*

***Metode**: Penelitian ini adalah studi potong lintang, dilakukan pada kelompok ibu hamil dengan ancaman persalinan prematur dan ibu hamil prematur di RSUP Prof. Dr. R.D. Kandou Manado dan RS jejaring, mulai Agustus 2016 sampai dengan Oktober 2016. Data dianalisis dengan SPSS versi 20 untuk melihat tingkat kemaknaannya.*

***Hasil**: Dari 16 ibu hamil dengan ancaman persalinan prematur dan 16 ibu hamil dengan hamil prematur, pada uji statistik t-test menunjukkan bahwa ada perbedaan yang bermakna kadar rata-rata sialidase vagina antara kelompok ancaman persalinan prematur dan kelompok hamil prematur (p=0,000).*

***Kesimpulan**: Ada hubungan antara kejadian ancaman persalinan prematur dengan kadar sialidase vagina.*

[Maj Obstet Ginekol Indones 2018; 6-1: 23-27]

***Kata kunci**: ancaman persalinan prematur, bakteri, sialidase vagina*

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INTRODUCTION

Preterm labour remains an important cause of perinatal morbidity and mortality in developing countries. Preterm labour, especially those that occur before 34 weeks' gestation, leads to ¾ of overall mortality in neonates. The infant mortality rate of preterm and very preterm (gestational age <32 weeks) were 15 and 75 times higher than babies born aterm. Premature infants who survive will suffer serious morbidity short terms, such as respiratory distress syndrome, bronchopulmonary dysplasia, interventricular haemorrhage, retinopathy of prematurity result, whereas at the long term, such as developmental disorders and neurological disorders. The morbidity rate may be reduced by doing a prevention of preterm birth procedure such as early and accurate predictions, eliminate the risks and delay the onset of labour to do an intervention using various treatments such as tocolytic, corticosteroids, and antibiotic prophylaxis. One pathogenic process of premature labour is inflammation.[1]

Pregnancy (gravidity) is called at term if between 37 - <42 weeks since the beginning of the last 28 days menstrual cycle. According to WHO preterm labour is labour that occurs between the ages of 20 weeks to about 37 weeks of the beginning of the last menstrual cycle (28 days).[2] In this context, developing countries have a higher incidence rate than developed countries. For the past 10 years, the incidence of BBLR hospitals nationwide was 27.9%. Approximately, the birth

rate in Indonesia is 5000.000 people per year, which could be calculated into infant mortality 56/1000 live births, equal to more or less 280,000 per year.[3]

Approximately 50% of the causes of preterm labour are unknown, and about 12.5% of preterm birth was preceded by premature rupture of membranes, wherefore, mostly due to factors of infection.[4] One basic pathogenesis of preterm labour is inflammation. From all of the etiopathogeneses, the most common cause of preterm labour is an infection, which means that the process of infection in the vagina and cervix (genital tract) may damage the vaginal mucosa and cervical barrier, thus bacteria can reach the uterus. In the vaginal mucosa consists of mucus glycoproteins (mucin) containing an antibacterial such as IgA, lactoferrin, and lysosomes. All this is contained in the surface epithelium of the vagina and cervix. In state of infection, mucus enzymes, digesting enzymes, were produced by bacteria such as sialidase, β-Galactosidase, β-N-Acetyl-hexosaminidase, a mucinous enzyme. This sialidase enzyme that can damage the vaginal mucosa and cervix into the uterus resulted in bacteria. Sialidase enzyme is also elevated in bacteria that colonise in the vagina. Sialidase produced by bacteria would lower the immunity of the vagina. Sialidase may potentially lower vaginal mucosal protective factors such as mucin, cytokines, immunoglobulins, antimicrobial molecules, and immune cell receptors.[5]

Howe and Wiggins reported that the levels of vaginal sialidase could be used to detect the presence of genital infections as well as the possibility of preterm labour in pregnant women. In this research, it concluded that the increased enzyme sialidase (BSM, $p < 0.005$).[6]

To this date, studies regarding have never been done at the department of Prof. Dr. R.D. Kandou Manado. This study is aimed to investigate the predictors of preterm labour at Prof. Dr. R.D. Kandou Manado.

METHODS

This was across-sectional study between the threatened of premature labour group and the premature pregnant group that conduct at RSUP Prof. Dr. R.D. Kandou Manado and its network hospital. Generally, this research aims to comprehend the connection between vaginal sialidase levels with the threatened of premature labour.

The research was conducted at RSU Prof. Dr. R.D. Kandou and its hospital networks in Manado from August 2016 to October 2016. From the sample, based on data collection, it obtained a total sample of 16 groups with the threatened of preterm labour and 16 groups of preterm pregnant women who meet the inclusion and exclusion criteria. Examination of a vaginal swab to detect the enzyme sialidase vagina.

Subjects were all pregnant patients under threatened of preterm labour and preterm pregnant women with normal pregnancies who meet the inclusion and exclusion criteria. The sample is part of a selected population, which includes all pregnant patients prematurely with the threatened of preterm labour and preterm pregnant with normal pregnancies were examined at the obstetric department of Prof. Dr. R.D. Kandou Manado and its hospital networks. The research subject took a vaginal swab for a sample to be determined through the rejection and acceptance criteria.

A set of acceptance criteria for the research sample were patients agreed to participate in the study, patients with prematurity (gestation less than 37 weeks) with infants <2,500 gram, mother who threatened preterm labor (pregnancy less than 37 weeks) with infants <2,500 gram, possess a valid information when the day her last menstrual period (LMP), and single-fetus pregnancies either ultrasound or physical examination.

Whereas, the rejection criteria for the research sample were patients who did not know their last menstrual period (LMP), pregnant patients with gestational multiple, polyhydramnios, congenital anomalies of the fetus, pregnant patients with anaemia: Hb <10 g / dl, has a systemic infection, diabetes, hypertension, liver disease, kidney, and malignancy, suffered an amniotic premature rupture membrane.

Patients who met the inclusion criteria and then examined the levels of enzyme sialidase vagina by way of vaginal swab results for vaginal swab is inserted into the transport tube and then examined using neuraminidase kit. Quantitative Examination

of the vagina with sialidase levels spectrophotometrically, a sensitivity of 1.0 pg/ml using a human sandwich kit neuraminidase (NEU) Elisa kit catalogue: MBS720861.

Each patient would be enrolled in this research adjusted to the principles of research ethics, that every pregnant woman premature enrolled in this study will be conducted counselling before hand with an explanation of the purpose and objectives of this research. If you agree, then the candidate must sign an agreement research study.

Analysis and data processing were carried out by the authors under statistics supervisor. Meanwhile, the data collection will be carried out by the researcher. It is executed both manually and computerised by using the software program Statistical Product and Service Solution (SPSS) for Windows version 20.

RESULTS

After effectuating research in RSU Prof. Dr. R.D. Kandou Manado and hospital networks in Manado from August 2016 to October 2016. This study has examined 16 pregnant women with threatened of preterm labor and 16 pregnant women with premature pregnancy.

The results of this study are presented below.

Table 2. Data Distribution of Vaginal Sialidase levels

Parameter Sialidase Vagina (ng/ml)	Premature Gestation (n=16)	Preterm Labour Threat (n=16)
Mean	245.46	710.16
Minimum	109.83	22.76
Maksimum	472.44	1432.43
p Normalitas	0.389	0.104

Table 3. Results of Relations Vaginal Sialidase Levels

Parameter	Sialidase Vagina Levels (ng/ml)		
	Mean	SD	p
Threatened of Preterm Labour	710.16	291.02	0.000
Premature Pregnancy	245.46	104.21	0.000

Table 1. Research Subject Characteristic

Variabel	Premature Gestation n (16)	(%)	Preterm Labour Threat n (16)	(%)
Age				
< 20	1	6.25	6	37.5
21 - 24	2	12.5	2	12.5
25 - 29	2	12.5	2	12.5
30 - 35	8	50.0	4	25.0
≥ 35	3	18.75	2	12.5
Parity				
Primigravidity	2	12.5	5	31.25
Multigravidity	14	87.5	11	68.75
Education				
Bachelor	2	12.5	1	6.25
High school	11	68.75	13	81.25
Junior High school	3	18.75	1	6.25
Primary School	0	0	1	6.25
Occupation				
Employee	6	37.5	2	12.5
Housewife / Unemployee	10	62.5	14	87.5
Age Pregnancy				
28 - 32	7	43.75	9	56.25
32 - <37	9	56.25	7	43.75

DISCUSSION

It appears that the level of sialidase on the threatened of premature labour group is higher than the sialidase levels in the premature pregnant group. Furthermore, the average level of sialidase vagina on the threatened of preterm labour group was higher than premature pregnancy group (710.16 pg / ml and 245.46 pg/ml). It means that the highest value of vaginal sialidase levels in the group of the threatened of preterm labour is higher than the group of preterm pregnancy (1432.43 pg/ml and 472.44 pg/ml). Whilst, levels were lowest in the group threatened of preterm labour of 22.76 pg / ml and in the group of premature pregnancy 109.83 pg/ml. Test normality of the data distribution vaginal sialidase levels is done by using the Shapiro-Wilk test at the significance level of 0.05, based on the test data is normally distributed vaginal sialidase levels ($p > 0.05$). It is seen that the levels of vaginal sialidase can also be detected in the case normally of premature pregnancy. According to the report Ann MB, et al (1992), which concluded that elevated levels of sialidase vagina were detected in 42 women (84%) of the 50 women whose vaginal discharge containing the bacteria (bacterial vaginosis) compared to 19 women vaginal discharge does not contain bacteria / do not suffer from bacterial vaginosis ($p < 0.001$). The vaginal fluid of women who have bacterial vaginosis has sialidase levels of around 9.8 u compared with 2.5 u in women who do not suffer from bacterial vaginosis. And the source of the activity of this enzyme is produced by the species of Bacteroides and Prevotella in the vagina.[7]

Analysis of the relationship between the vaginal sialidase levels of threatened of preterm labour groups and premature pregnancy groups was performed using the test towards variable t (independent variable), it can be concluded whether there were significant differences between vaginal sialidase levels in the group with preterm pregnancy compare to the group with the threatened of premature labour. Based on a result of the test towards variable t, there were significant differences between the two groups, $p < 0.000$. So it can be concluded there is a correlation between the incidence threatened of preterm labour with vaginal sialidase levels. In this research, vaginal sialidase levels increased due to an inflammatory process that produces the vaginal sialidase enzyme on vaginal passage. In the state of infection mucus enzymes digesting enzyme produced by bacteria such as sialidase, β-Galactosidase, β-N-Acetylhexosaminidase, enzymes mucinous. Sialidase potentially lowering vaginal mucosal protective factors such as mucin, cytokines, immunoglobulins, antimicrobial molecules, and immune cell receptors.[5]

Howe and Wiggins reported that the levels of vaginal sialidase can be used to detect the presence of genital infections and detecting the possibility of preterm labour in pregnant women.[6] Furthermore, Zang, et al (2002) compared the 80 pregnant women with bacterial vaginosis and 60 normal pregnant women at the same gestational age, then an examination of vaginal sialidase, concluded that there were significant differences between the two groups, $p < 0.0001$.[8] Moreover, Cauci, et al (2011) in its analysis said that an increase in vaginal sialidase levels was measured at 12 weeks of pregnancy was associated with increased incidence of premature labour and increased levels then increased the incidence of premature labour.[5]

In a research report; Howe, et al (1999) indicate that the mucinase activities and sialidase on vaginal microflora is an implication of the labor / threats of premature to conclude that the 31 pregnant women with vaginal infections and tests of enzyme activity hydrolase, there is increased activity of the enzyme significant enzyme sialidase in women with labor/threatened of preterm labour to the statistical test ($p < 0.005$).[6]

The most optimal sensitivity value (93.8%) and specificity (100%). Above results in accordance with Bradshaw, et al (2005) in its report on the evaluation of the test in women with bacterial vaginosis using detection devices that the enzyme sialidase test tool show sensitivity at 88%, 95% CI (81-93%) levels, and specificity figures 95%, 95% CI (91-98%) compared with conventional case.[9] Whereas, the examination of Zang, et al (2002) compared the 80 pregnant women with bacterial vaginosis and 60 normal pregnant women at the same gestational age, and then examined the levels of vaginal sialidase the results of a sensitivity 96.7% and specificity of 97.5%.[8]

Cauci, et al (2011) in its research report indicate the number sialidase levels > 5 nmol, > 10 nmol, > 14 nmol associated with a significant incidence of early preterm birth.[5] In accordance with that, Marconi, et al (2013) stated that the levels of

sialidase vaginal bacterial vaginosis state showed the highest rate of 800 ng/ml.[10] Whilst, In this research the highest number 1433.43 pg/ml (143.343 ng/ml). Sanita C, et al (2015) also reported that 35 of the total 52 pregnant patients with bacterial vaginosis were detected in the presence of enzyme activity levels of the enzyme sialidase with a median of 10.3 ng/ml (range 0.0-163.3 ng/ml) were correlated with preterm labour and membranes ruptured.[11] In this study, vaginal sialidase levels in threatened of preterm labour median result of 736.41 pg/ml (73.641 ng/ml). The results of these studies support the conclusion that the bacteria associated with an enzyme that affects the mucosal barrier that can provide entry for bacteria into the reproductive tract that will cause a local infection in the birth canal.

CONCLUSION

There is a difference in meaning between the threatened of preterm labour and premature delivery group. So it can be concluded that there is a correlation between the incidence threatened of preterm labour with vaginal sialidase levels.

RECOMMENDATION

Vaginal sialidase levels may be one of the early predictors threatened of preterm labour case. It is important to do a further research with more samples and evaluation of outcomes of pregnancy also is necessary to breed the bacteria that produce the type of hydrolase enzymes in threatened of preterm labour that can be used to support the process of infection that may act as the cause of their state of prematurity.

REFERENCES

1. Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, et al. Screening to prevent spontaneous preterm birth : systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess. 2009; 13: 43.
2. Norman J, and Greer I. Preterm labour : Managing risk in clinical practice. N Engl J Med. 2006; 355: 742.
3. Kementerian Kesehatan RI. Profil Kesehatan Indonesia 2014. Yudianto, Budijanto D, Hardhana B, Soenardi TA, editors. Jakarta: Kementerian Kesehatan RI; 2015: 1-188.
4. Moutquin JM. Classification and heterogenity of preterm birth. Int Obstet Gynecol. 2003; 110(20): 30-3.
5. Cauci S, Culhane JF. High sialidase levels increase preterm birth risk among women who are bacterial vaginosis-positive in early gestation. Am J Obstet Gynecol. 2011; 204(2): 142.e1-9.
6. Howe L, Wiggins R, Soothill PW, Millar MR, Horner PJ, Corfield AP. Mucinase and sialidase activity of the vaginal microflora : implications for the pathogenesis of preterm labour. Int J STD AIDS. 1999; 10(7): 442-7.
7. Briselden AM, Moncia BJ, Stevens CE, dan Hillier SL. Sialidases (neuraminidases) in bacterial vaginosis and bacterial vaginosis-associated microflora. J Clin Microbiol. 1992; 30(3): 663-6.
8. Zhang X, Xu X, Li J, Li N, Yan T, danJu X. Relationship between vaginal sialidase bacteria vaginosis and chorioamnionitis. Zhonghua Fu Chan KeZaZhi. 2002; 37(10): 588-90.
9. Bradshaw CS, Morton AN, Garland SM, Horvath LB, Kuzevska I, dan Fairley CK. Evaluation of a Point of Care Test, BVBlue, and Clinical and Laboratory Criteria for Diagnosis of Bacterial Vaginosis. J Clin Microbiol. 2005; 43(3): 1304-8.
10. Marconi C, Donders GGG, Bellen G, Brown DR, Parada CMGL, dan Silva MG. Sialidase activity in aerobic vaginitis is equal to levels during bacterial vaginosis. Eur J Obstet Gynecol Reprod Biol. 2013; 167(2): 205-9.
11. Ferreira CS, Marconi C, Parada CM, Duarte MT, Goncalves AP, Rudge MV, et al. Bacterial vaginosis in pregnant adolescent :pro-inflammatory cytokine and bacterial sialidase profile: cross sectional study. Sao Paulo Med J. 2015; 133(6): 465-70.

Research Article

Internet Based Infertility Information in Bahasa Indonesia Quality Survey

Survei Kualitas Informasi Infertilitas pada Situs Internet Berbahasa Indonesia

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Abstract

Objective: To assess the quality of websites providing information on infertility and its management in Bahasa.

Methods: Differences between website types and affiliates were assessed for the credibility, accuracy and ease of navigation using predefined criteria. We used Google search engine with the keyword "infertilitas" and we assessed 50 websites in Bahasa that relates with infertility.

Results: The content credibility for most of the sites has adequate score with range of score 60 to 80 for 68% sites. Content accuracy for most of the sites have scores more than 60, with 24% or 12 sites with scores 60 to 80 and 44% or 22 sites have scores above 80. The ease of navigation for most of the sites, 47 sites or 94% has scores more than 60.

Conclusion: The quality of internet based infertility information in Bahasa is adequate for category credibility, accuracy and ease of navigation.

[Indones J Obstet Gynecol 2018; 6-1: 28-33]

Keywords: bahasa, infertility, information, internet, quality

Abstrak

Tujuan: *Untuk mengetahui gambaran kualitas isi informasi di internet mengenai infertilitas pada situs berbahasa Indonesia.*

Metode: *Penelitian ini menggunakan desain potong lintang. Melalui mesin pencari Google dengan kata kunci infertilitas, kemudian dipilih lima puluh teratas situs internet berbahasa Indonesia. Kemudian dilakukan identifikasi dan dikelompokkan berdasarkan kategori penulis, domain dan komersialisasi. Situs kemudian dilakukan telaah mengenai kredibilitas, akurasi dan kemudahan navigasi sesuai dengan criteria pada definisi operasional.*

Hasil: *Kredibilitas konten tentang infertilitas pada studi ini didapatkan sebagian besar situs yang dilakukan survei memiliki nilai skor kredibilitas yang memadai dengan rentang skor kredibilitas 60 hingga 80 pada 68% situs. Akurasi konten tentang infertilitas pada studi ini didapatkan sebagian besar situs memiliki skor akurasi yang baik yaitu sebanyak 12 situs atau 24% dengan skor 60 hingga 80 dan 22 situs atau 44% dengan nilai skor di atas 80. Kemudahan navigasi pada situs internet berbahasa Indonesia mengenai infertilitas, pada studi ini didapatkan sebagian besar situs memiliki navigasi yang mudah dengan skor total kemudahan navigasi di atas nilai 60 sebanyak 94% atau 47 situs.*

Kesimpulan: *Sebaran kualitas isi informasi mengenai infertilitas pada situs internet berbahasa Indonesia memadai dari aspek kredibilitas, akurasi dan kemudahan navigasi.*

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Kata kunci: *bahasa, infertilitas, informasi, internet, kualitas*

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INTRODUCTION

Infertility in Indonesia is a unique and complex problem as it involves various cultural backgrounds and beliefs in the society. Information related to infertility is a sensitive and personal issue due to negative stigma to infertile partners. Thus, the access and reliability of the information related to infertility becomes paramount.[1]

There is no difference between the infertile couples and other Internet users. A survey conducted to 200 infertile couples showed that some of these couples utilized the Internet to obtain more information related to infertility. In addition, two third of female users were highly influenced by the information that they got from the Internet to find a solution to infertility.[2]

Nowadays, the Internet is a part of everyone's life. Many information could be easily accessed through the Internet including health topics. A study conducted by the Internet World Statistics (2007) revealed that two third of the UK population used the Internet. Meanwhile, a survey conducted by the Harris Poll Group (2007) suggested that 60-80% of Internet users search

information related to their health and the management choices to refer to.[3] There were 91% of infertile couples that searched informations related to their conditions from the search engine. Information related to infertility can be accessed through search engine such as Google™ and Yahoo™.

In Indonesia, studies related to the health information quality from the Internet, especially those that are related to infertility, have never been conducted. On the other hand, cyberspace through social media today is used as source of information especially for adolescences and those in reproductive ages.[4] Therefore, there is a need on conducting researches related to the quality of information provided in Bahasa Indonesia from the Internet.

METHODS

This was a cross-sectional study. Using the keyword "infertility" through Google™ as the search engine, fifty Indonesian language websites are included. Subsequently, further identification and cluster on the websites were conducted based on the categories of the writers, domains and commercial purposes. This study was continued to comprehend the credibility, accuracy and ease on navigation on the basis of the criteria in relation to the operational definition.

RESULTS AND DISCUSSION

A total of 60 patients were recruited in this study. Data collection was conducted during the period of January 1st, 2016 to April 1st, 2016. The study was managed through Google with the keyword "infertilitas". In this study, we found fifty websites in Bahasa Indonesia with the topic of infertility. These websites were grouped based on the category of the writers that were written by individuals, health organization and non-health organization. The sites were managed based on the domain types, including .com, ac.id, .org, .blog, .co and .net. Further classification was also conducted based on commercial and non-commercial purposes. (Table 1) From Google as the search engine and the keyword "infertility", first website to appear was a non-commercial website followed by commercial website as the third rank.

Table 1. Websites Charateristics in Bahasa Indonesia

Characteristic	**N (%)**
Category of writers	
Individual	11 (22)
Health organization	30 (60)
Non-health organization	9 (18)
Type of domain	
.com	22 (50)
.ac.id	4 (8)
.blog	14 (28)
.co	4 (8)
.net	5 (10)
.org	1 (2)
Commercial purposes	
Commercial	11 (22)
Non-commercial	39 (78)

Generaly, the websites appraisal related to their credibility and accuracy could be improved, but the user-friendly navigation of the sites had good scores. In the credibility category, all groups performed good scores referring to six criteria including authors, an up to date information, statements, peer-reviewers, and commercial purposes by having advertisements and sponsors. Name of the authors were found in 58% or 29 sites, while 54% (29 websites) were found to be updated related to infertility information. In general, scores of other categories such as statements and peer-reviewer were low by only 4% (2 sites) in combination. On the other hand, there were 60% (30 sites) that had commercial on their sites, while 24% (12 sites) with sponsors.

Appraisal in relation to the accuracy of the sites includes two categories, which are coherency and references. Overall, there were 22 sites (44%) following the guideline, whereas only 10 sites (20%) that put the references. Ease of site navigation consist of six categories, including internal and external links, links to external website, feedback form, frequently asked questions, sitemaps and built-in search engine. There were 96% (48 sites) have internal and external links and sitemaps. Moreover, 76% (38 sites) had built-in search engines, 58% (29 sites) had feedback form, 8% (4 sites) including frequently asked questions, and only 6% (3 sites) have external directed links. (Table 2)

Table 2. Websites Charateristics of Credibility, Accuracy and Ease to Navigate

Characteristics	N (%)
Credibility	
Author	44 (88)
Update information	42 (84)
Statements	27 (54)
Peer-review	31 (62)
Advertisements	40 (80)
Sponsors	36 (72)
Accuracy	
Guidelines	38 (76)
Reference	34 (68)
Ease to navigate	
Internal and external links	49 (98)
Redirect link	28 (56)
Feedback	35 (70)
Frequently asked questions	30 (60)
Sitemaps	50 (100)
Search engine	46 (92)

Medical information in regard infertility were classified to eight topics, which were definition, causes of infertility, pathogenesis of infertility, diagnosis of infertility, medical treatment, procedural management, prevention and psychological aspects of infertility. (Table 3)

Table 3. Websites Characteristics based on Medical Information Contain

Characteristic	N (%)
Definition	50 (100)
Cause	49 (98)
Pathogenesis	21 (42)
Diagnosis	36 (72)
Medical treatment	37 (74)
Procedural management	16 (32)
Prevention	17 (34)
Psychological management	16 (32)

Internet Site Score in Bahasa Indonesia

Overall score from three categories above (credibility, accuracy and ease to navigate) are above 60 in total. The scores of credibility from 34 sites were in the range of 60 to 80, while six sites had the score of 80 to 100. The last ten sites scores were below 60.

In this category of accuracy, there were 12 sites which obtained total score of 60 to 80 and 22 sites obtained total score of 80 to 100. 16 of the sites obtained total score of less than 60.

In this ease of navigation category, there are some sites with ease of navigation score above 60. There were 22 sites which obtained score of 60 to 80 and 25 sites which obtained total score of 80 to 100. Only minority of the sites (5 of them) obtained total score of less than 60.

Comparison of Total Average Score

Total Average Score Comparisons

There is not much difference in total average score of credibility and accuracy categories between websites that come from medical organizations and non-medical organizations. Statistically, there were not much of substantial difference between the three categories of average score of credibility ($p=0.550$), accuracy, ($p=0.563$), and ease of navigation ($p=0.305$) within both groups. There were significant differences in average score of accuracy and navigation between .com sites and ac.id sites. In the category of credibility, there are not much considerable differences with score of $p > 0.05$. On the other hand, in the category of accuracy and navigation there were substantial differences with each having score of $p < 0.01$ in the category of accuracy and $p = 0.047$ for the ease of navigation. Both categories of accuracy and navigation. For both categories of accuracy and navigation, there were not much differences with each having score of $p < 0.01$ in accuracy and $p = 0.047$ for ease of navigation. There were not much differences in total score of accuracy and navigation categories with the score of $p > 0.05$. In the category of credibility, there was noticeable difference statistically between commercial and noncommercial websites with $p = 0.002$.

The accuracy of information in websites about infertility is one of issues which are now the topic of discussion.[5] Nevertheless, with this research, there are 16 sites that have total accuracy score of less than 60. This research is different with earlier Studies by Jain and Barbieri regarding the quality of information about infertility on the Internet, especially regarding the accuracy of presented information.[5,6] The difference is perhaps connected to the criteria of accuracy measurement used in this study is different with previous studies.[7] in this study, the criteria of accuracy used are when there are matches between provided information with clinical guide and the displaying of library resources.[8] Other than that, the limit of the score used in this study was 60, the difference in appraisal of information from the websites could also be caused by the difference in limit of score provided between the studies.[9]

Related to the accuracy of information in the websites, there are very few sites that display the study of a library resources.[10] while the process mentioned is critical to determine whether a publicized study is suitable to use as a resource.[11] This shows that minimal regulation related to publication will affect the credibility of the information. Thus may lead the website users to wrong decision related to their infertility. Comparing all category, ease to navigate received the highest score with most websites (47 sites) in above 60.[12] There were only three sites graded below 60. The result of this study is in line with previous study by Eipstein and Rosenberg, 2005, who stated the ease to navigate of a website will increase the accuracy and credibility of the information.[13,14]

In this study, there were more websites written by health organization (60% or 30 websites) compared to individual (11 websites) or non-health organization (9 websites). Moreover, from top 50 search by Google, websites from health organization were dominating the outcome. On the other hand, a study conducted by Marriot et al, 2008, showed different result with the users or the site were mainly non-health organization.

From the domain types, measuring from category of accuracy and ease to navigate, there was a significant difference between .com domain and ac.id domain. The .com domain had lower mean score for both measurement mentioned. The reason behind is because those websites are mostly from non-health organization and commercialized compared to the ac.id domain.[15] This same result was showed by a research by Huang et al, 2005 and Selman et al, 2006 that stated the websites from non-health organization had lower credibility and accuracy compared to the websites written by health organization.[2,15] Based on these studies, the information from the health organization websites were more comprehensive, thus more helpful for the readers. Moreover, non-commercial websites had lower mean scores compared to commercial websites, measured from three categories (credibility, accuracy and navigation). There was a significant difference in the website credibility category.

Based on the studies by Huang et al, 2005 and Jain and Barbieri, 2005, readers were having their concern related to the content quality from commercial websites. Therefore, it affects the overall content of the sites.[16,17] These differences will have impacts on the credibility and accuracy of infertility information. A study by Marriot found that websites from health organization were less accessible compared to those from non-health organization despite of specific keywords entered.[18] In this study, the key word used was "infertility", therefore websites that appear in top 50 mainly came from healthcare organizations. The word infertility was more popular in the field of medicine compared to other phrases like "intrusion of fertility". The influence of choosing the keyword in regards to searching for websites was apparently significant in the results of the websites and the source of the websites, thus the choice of keywords is critical to assess the credibility and the accuracy of the websites. The study by Ellsworth and Ellsworth in 1996 says that websites from healthcare organizations fail to fulfil the strategy of electronic commerce which leads to websites from medical organizations lacking popularity the findings are similar with the result of the study by Theodosiou and Green 2003 along with Selman and friends, 2006.[5,19] This fact is surely being one of the causes of websites from non-medical organizations are more well-known compared to websites from medical organizations. Contrary to this study, websites that came from medical organizations earned higher sum and higher ranking compared to websites from non-medical organizations. This might be due to less information in websites from non-medical organizations regarding to infertility. Thus, more

websites from medical organizations were more popular compared to non-medical organizations.[20] We found that there were not much of substantial differences statistically between the categories of credibility, accuracy and ease of navigation from the type of writers on websites which were divided into writers that come from medical organizations and writers that come from non-medical organizations.[21]

Another study by Marriot, 2008, found that health organization credibility score was better compared to non-health organization. The possible underlying factor is the number of individual writers from the non-health organization have good credibility and accuracy score. Therefore, the difference between health and non-health organization websites did not show any significant difference.

CONCLUSION

There is a moderate quality of infertility websites information in Bahasa Indonesia analyzed from aspects of credibility, accuracy and ease to navigate. However, there were difficulties in assessing the quality content by using the current scoring criteria.[22] Although the scoring criteria is comprehensive, it is only an indirect measurement of the websites content.[23] In the future, we expect better scoring system that can represent three aspects for the assessment.

RECOMMENDATION

Moreover, further study needs to be conducted to have better quality assessment for the weight of score for each criterion. Hereinafter, there should be an assurance of the credibility and accuracy of information related to infertility provided in Bahasa Indonesia. For further research, we suggest that health resources to advices to the readers to browse a credible and accurate websites in Bahasa Indonesia based on the criteria that was previously accepted.[24]

REFERENCES

1. Abusief ME, Hornstein MD, Jain T. Assessment of United States fertility clinic websites according to the American Society for Reproductive Medicine (ASRM)/Society for Assisted Reproductive Technology (SART) guidelines. Fertil Steril. 2007; 87(1): 88-92.
2. Huang JYJ, Al-Fozan H, Tan SL, Tulandi T. Internet use by patients seeking infertility treatment. Int J Gynecol Obstet. 2003; 83(1): 75-6.
3. Marriott JV, Stec P, El-Toukhy T, Khalaf Y, Braude P, Coomarasamy A. Infertility information on the World Wide Web: a cross-sectional survey of quality of infertility information on the internet in the UK. Hum Reprod. 2008; 23(7): 1520-5.
4. Laksono AD WR. Analisis Potensi Penyebaran Informasi Kesehatan Melalui Jejaring Sosial (Studi Kasus Pada "Forum Jejaring Peduli AIDS"). Bul Penelit Sist Kesehat[Internet] [Internet].[http://bpk.litbang.depkes.go.id/index.php/hsr/article/view/1373 p.].
5. Jain T, Barbieri RL. Website quality assessment: Mistaking apples for oranges. Fertil Steril. 2005; 83(3): 545-7.
6. Winkelman WD, Katz PP, Smith JF, Rowen TS. The Sexual Impact of Infertility Among Women Seeking Fertility Care. Sex Med. 2016; 4(3): 190-7
7. Kahlor L, Mackert M. Perceptions of infertility information and support sources among female patients who access the Internet. Fertil Steril. 2009; 91(1): 83-90.
8. The evolving e-practice. Practice website design and marketing: integrating Internet services. Prac Procedures Aesthetic Dentistry : PPAD. 2007; 19(7): 416-8.
9. Botvin JD. Web site review. Carolinas Health Care recognized Internet marketing potential early. Profiles in healthcare marketing. 2005; 21(5): 24-30, 3.
10. Gray SW, Cronin A, Bair E, Lindeman N, Viswanath V, Janeway KA. Marketing of personalized cancer care on the web: an analysis of Internet websites. J Nat Cancer Inst. 2015: 107(5).
11. Buis LR. The potential for web-based social network sites and self-regulation for health promotion. American journal of health promotion: AJHP. 2011; 26(2): 73-6.
12. Rothschild MA. Marketing your practice on the Internet. Otolaryngol Clin North Am. 2002; 35(6): 1149-61.
13. Epstein YM, Rosenberg HS. Assessing infertility information on the Internet: challenges and possible solutions. Fertil Steril. 2005; 83(3): 553-5.
14. Aslani A, Pournik O, Abu-Hanna A, Eslami S. Web-site evaluation tools: a case study in reproductive health information. Studies in health technology and informatics. 2014; 205: 895-9.
15. Provost M, Koompalum D, Dong D, Martin BC. The initial development of the Web Med Qual scale: domain assessment of the construct of quality of health web sites. Int J Med Informatics. 2006; 75(1): 42-57.
16. Ditto S, Pille B. Marketing on the Internet. Healthcare Executive. 1998; 13(5): 54-5.
17. Ellsworth J EM. Marketing on the Internet-Multimedia Strategies for the WWW. New York: John Wiley & Sons; 1996.
18. Seale C. Portrayals of treatment decision-making on popular breast and prostate cancer web sites. Eur J Cancer Care. 2005; 14(2): 171-4.
19. Theodosiou L, Green J. Emerging challenges in using health information from the internet. Advances in Psychiatric Treatment. 2003; 9(5): 387-96.
20. Davidoff F, Batalden P, Stevens D, Ogrinc G, Mooney S. Publication guidelines for quality improvement in health care: evolution of the SQUIRE project. Quality & safety in health care. 2008; 17 Suppl 1: i3-9.

21. Zhang GQ, Cui L, Teagno J, Kaebler D, Koroukian S, Xu R. Merging Ontology Navigation with Query Construction for Web-based Medicare Data Exploration. AMIA Joint Summits on Translational Science proceedings AMIA Summit on Translational Science. 2013; 2013: 285-9.
22. Chang SG, Kim DI, Shin ES, Jang JE, Yeon JY, Lee YS. Methodological Quality Appraisal of 27 Korean Guidelines Using a Scoring Guide Based on the AGREE II Instrument and a Web-based Evaluation. J Kor Medical Scien. 2016; 31(5): 682-7.
23. Meric F, Bernstam EV, Mirza NQ, Hunt KK, Ames FC, Ross MI, et al. Breast cancer on the world wide web: cross sectional survey of quality of information and popularity of websites. BMJ. 2002; 324 (7337): 577-81.
24. Veronin MA. Where are they now? A case study of health-related Web site attrition. J Med Internet research. 2002; 4(2): E10.

Research Article

Pregnancy Outcome in Infertility Patient with Endometriosis Cyst after Laparoscopic Cystectomy

Luaran Kehamilan pada Pasien Infertilitas dengan Kista Endometriosis yang Dilakukan Laparoskopi Kistektomi

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Abstract

Objective: To investigate about the rate of pregnancy in women who had undergone laparoscopic cystectomy.

Methods: This was a retrospective study. Data were taken from the medical records of patients with infertility in Fatmawati Hospital, Jakarta, Indonesia. Data then analyze to know is there any association between age, infertility duration, bilaterality of the cyst, tubal patensy, r-AFS stage with pregnancy rate.

Results: A total of 64 subjects were recruited in this study. There were 23 subjects (35.9%) that got pregnant within one year after undergoing laparoscopic procedure. Those who were 35 years old or less had a greater chance to get pregnant (p = 0.01, OR = 6.75), duration of infertility ≤ 3 years had a greater chance to get pregnant with OR = 3.2 and p value = 0.032, r-AFS stage II and III had a greater chance to get pregnant to with (p = 0.04, OR = 3.25 and 4.25).

Conclusion: The pregnancy rate after laparoscopic procedure is 35.9% in this study. There are correlation between age, duration of infertility, and r-AFS staging with pregnancy rate.

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Keywords: endometriosis, infertility, laparoscopy, pregnancy

Abstrak

***Tujuan**: Untuk mengetahui persentase pasien endometriosis dengan infertilitas yang hamil dalam waktu satu tahun pasca-prosedur laparoskopi dan faktor-faktor yang mempengaruhinya.*

***Metode**: Penelitian ini merupakan studi kohort retrospektif, sumber data berasal dari rekam medis dengan pendekatan penelitian deskriptif-analitik kategorikal dengan menggunakan rekam medik pasien yang dilakukan laparoskopi di Rumah Sakit Fatmawati, kemudian di follow up untuk mengetahui kejadian kehamilannya. Data kemudian dianalisis untuk mengetahui hubungan antara usia, lama infertilitas, bilateralitas kista, patensi tuba, dan derajat r-AFS dengan kehamilan.*

***Hasil**: Terdapat 64 subjek yang dianalisis. Sebanyak 23 subjek (35,9%) hamil dalam satu tahun pasca laparoskopi. Kelompok usia ≤ 35 tahun memiliki peluang untuk hamil lebih besar dengan OR 6,75 dan nilai p=0,01, lama infertilitas ≤ 3 tahun memiliki peluang untuk hamil lebih besar dengan OR 3,2 dan nilai p=0,032, derajat r-AFS II dan III juga memiliki peluang hamil yang besar dengan OR 3,25 dan 4,25 dengan nilai p=0,04.*

***Kesimpulan**: Pada penelitian ini didapatkan angka kehamilan dalam satu tahun pascalaparoskopi sebesar 35,9%. Terdapat hubungan antara usia, lama infertilitas dan derajat r-AFS dengan kehamilan.*

[Maj Obstet Ginekol Indones 2018; 6-1: 34-38]

***Kata kunci**: endometriosis, infertilitas, kehamilan, laparoskopi*

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INTRODUCTION

The World Health Organization (WHO) estimated that approximately 60-90 million couples had infertility problem or about 8-12% of all couple in the world. Endometriosis is one factor that causes infertility in female;[1] approximately 20-40% infertile women have endometriosis. Endometriosis prevalence in women in reproductive age is around 3-10%.[2,3]

Infertility in endometriosis can be caused by 3 main mechanism, including: disrupt ovum pick up by fimbriae due to adnexal anatomy alteration, interference of oocyte maturation or early embriogenesis, and decreased endometrial receptivity to zygote implantation.[4,5]

Infertility is correlated with disease severity. Woman with severe endometriosis have lower estrogen level, fewer oocyte, lower pregnancy and implantation rate than woman with mild endo-

metriosis. Abnormal oocyte quality and embriogenesis have a more role in decreasing pregnancy and implantation rate than decreased endometrial receptivity in woman with endometriosis.[6-8]

Laparoscopy is an important procedure to manage infertility that can be used to diagnostic or therapy. Laparoscopic adhesiolysis, resection, or ablation of endometrial lession, and cystectomy usually performed in endometriosis cases. Those procedures can increase fecundability in infertility woman.[9]

METHOD

This was a retrospective study. Data were derived from the medical records with categorical analyzis study to find pregnancy rate after laparoscopic cystectomy in infertility patient with endometriosis cyst in Fatmawati Hospital and it's association with age, duration of infertility, bilateral/unilateral cyst, tube patency, previous pregnancy, and r-AFS grade of endometriosis. This study was conducted in Fatmawati Hospital during 1st February 2016 - 30th December 2016.

Population target is infertility patient with endometriosis cyst that underwent laparascopic cystectomy in Indonesia. Accessible population is infertile patient with endometriosis cyst that underwent laparoscopic cystectomy in Fatmawati Hospital during 1st January 2011 - 31st December 2014.

Inclusion criteria were infertile women, had endometriosis, and had undergone laparoscopic cystectomy. Those who refused to participate in this study, had other conditions that cause infertility (leiomyoma uteri, adenomyosis, abnormal both tube, or PCOS) abnormal sperm analysis (Azoospermia, Teratozoospermia, or asthenozoospermia), did not want or plant to have a child after laparoscopic procedure, no valid phone number or address to contact the patient, and menopause. Sample size of this study is 65.

Data analyzed from total sample to get percentage of patient that pregnant in one year after cystectomy laparoscopic. Endometriosis grade defined from surgical report using r-AFS grading. This study have ethical clearance and location permission from Fatmawati hospital.

RESULTS

A total of 64 subjects were involved in this study. The mean age of the subjects was 32.5 ± 4.5 years old. The characteristics of the subjects are presented in Table 1. Chi square and Kolmogoro-Smirnov test were performed and the results are age (p=0.010), infertility duration (p=0.032), and r-AFS grade (p=0.010) have significant association with pregnancy rate within 1 year after laparoscopic cystectomy in infertility patient with endometriosis cyst. Odd ratio to each characteristic can be seen in table 1. Whereas previous pregnancy (p=0.153), non patent in one of tube (p=0.073), and endometriosis cyst bilaterality (p=0.082) did not have significant association with pregnancy rate after laparoscopic cystectomy in infertility patient with endomtriosis cyst.

Table 1. Association Infertile Patient with Endometriosis Cyst Characterisitc after Laparoscopic Cystectomy

Characteristic	Pregnant		Not pregnant		p	*OR*	*CI 95%*
	n	%	n	%			
Age							
≤ 35 y.o.	21	45.65	25	54.35	0.010[a]	6.72	1.29 - 65.22
36 - 39 y.o.	2	14.29	12	85.71			
40 y.o.	0	0	4	100			
Infertility duration							
≤ 3 years	11	55.0	9	45.0	0.032[b]	3.26	0.94 - 11.32
> 3 years	12	27.27	32	72.73			
Previous pregnancy							
Primary Infertility	4	22.22	14	77.78	0.153[b]	0.41	0.08 - 1.59
Secondary Infertility	19	41.30	27	58.70			

Characteristic	Pregnant		Not pregnant		p	OR	CI 95%
	n	%	n	%			
Bilaterality							
Unilateral	13	48.15	14	51.85	0.082[b]	2.51	0.78 - 8.16
Bilateral	10	27.03	27	72.97			
Tube patency							
One tube non patent	7	58.33	5	41.67	0.073[b]	3.15	0.72 - 14.40
Both tubes patent	16	30.77	36	69.23			
Grade r-AFS							
Grade II	6	66.67	3	33.33	0.010[b]	3.25[c]	0.64 - 16.43
Grade III	12	46.15	14	53.8		4.15[d]	1.15 - 15.03
Grade IV	5	17.24	24	82.76			

a = Kolmogorov-Smirnov test
b = Chi-square test
c = odds ratio grade II to grade IV
d = odds ratio grade III to grade IV

During follow up, 23 subject (35.94%) were pregnant. 9 of them (39.13%) were pregnant within 6 months as seen in Table 2.

Table 2. Pregnancy Rate within 1 Year after Laparoscopic Cystectomy in Infertility Patient with Endometriosis cyst

Interval	Frequency	%	95% CI
Pregnant	23	35.94	0.243 - 0.489
< 6 months	9	39.13	0.197 - 0.615
6-12 months	14	60.87	0.385 - 0.803
Not pregnant	41	64.06	0.511 - 0.757
Total	64	100	

The pregnancy outcome are presented in Table 3. From 23 subject that pregnant, 16 subject (69.56%) were end up with term pregnancy, 4 subjects (17.39%) were preterm birth, 1 subject (4.34%) had ectopic pregnancy, 1 subject (4.34%) had miscarriages, and 1 subject (4.34%) was IUFD.

Table 3. Pregnancy Outcome Infertility Patient with Endometriosis Cyst after Laparoscopic Cystectomy

Pregnancy outcome	Frequency	%	95% CI
Term	16	69.56	0.471 - 0.868
Preterm birth	4	17.39	0.049 - 0.388
Miscarriages	1	4.34	0.001 - 0.219
IUFD	1	4.34	0.001 - 0.219
Ectopic pregnancy	1	4.34	0.001 - 0.219
Total	23	100	

DISCUSSION

Association between endometriosis and infertility has attracted many attention. Laparoscopy is one of method that can be choose to treat endometriosis. Laparoscopy have a role to increase pregnancy rate in infertility patient with endometriosis. Meta analysis Cochrane reported laparoscopy could increase pregnancy rate by OR 1.66; 95%CI 1.09-2.51.[10] Marcoux et al, reported the pregnancy rate in 9 months after laparasccopy in endometriosis patient is 30.7%, while in control group is 17.7%.[11]

This study reported that pregnancy rate of infertilite patients with endometriosis cyst within 1 year after laparoscopic cystectomy is 35.94%, with 39.19% of them were pregnant within 6 months after laparoscopy. All subject that get pregnant within 6 month had r-AFS grade < IV and 88.89% of them were ≤ 35 years old.

This study result is lower than study by Lee et al (2013) that reported natural conception after laparoscopy in infertile women with endometriosis is 41.9% within first year, 66.7% of them pregnant within first 3 months and 94.4% of them pregnant within first 6 months.[12] Jacobson et al. (2014) reported with meta analysis that pregnancy rate within first 2 years after laparosopic procedure is 35.5% with 75% of them pregnant within first 12 months after procedure.[10]

Of study, there are numerous factors that could possibly associated with pregnancy rate after laparoscopic cystectomy in infertile patients with

endometriosis cyst. First factor is age, from this study, age divided into 3 group : ≤ 35 y.o., 36-39 y.o., and ≥ 40 years old. Pregnancy rate in ≤ 35 y.o. group is 45.65% compared to 14.29% in 36-39 y.o. group and 0% in ≥ 40 y.o. group with p value = 0.010. Therefore, we conclude that age ≤ 35 have higher chance to get pregnant after laparoscopic cystectomy in infertility patient with endometriosis cyst compared to age > 35 y.o. with OR = 6.72. Lee et al (2013) reported all patient who get pregnant are < 35 y.o. in age with sample age between 20-39 years old.[12] Adamson et al (2010) divided age into 3 groups : ≤ 35 y.o., 36-39 y.o., and ≥ 40 y.o. with higher score in lower ages.[13]

Infertility interval have significant association with pregnancy rate after laparoscopic cystectomy in infertility patient with endometriosis cyst. Adamson et al (2010) include interval infertility in endometriosis scoring system that divided into 2 group : ≤ 3 years and > 3 years.[13] This study, there is 55% subject in infertility interval ≤ 3 years group that pregnant within 1 year after laparoscopy compared to 27.27% ininfertility interval > 3 years group with p value=0.032 and OR 3.26.

Endometriosis grading r-AFS have significant association with pregnancy rate after laparoscopy in infertility patient with endometriosis cyst. About 55.6% subject in grade r-AFS II group get pregnant within 1 year after laparoscopy compared to 46.2% subject in grade r-AFS III group get pregnant, and 20.7% subject in grade r-AFS IV get pregnant with p value=0.040. Odds ratio between grade r-AFS II and r-AFS IV is 3.25, while odds ratio betweeen grade r-AFS III and r-AFS IV is 4.15. Those result showed that patient with grade r-AFS < IV have a higher chance to get pregnant after laparoscopy compared to those with grade r-AFS IV. Lee et al (2013) reported there is no proportional association between AFS endometriosis grading with pregnancy rate, but reported that AFS IV have lower rate compared to others (grade I 35.7%, grade II 44.4%, grade III 53.3%, and grade IV 20.0%).[12] It is correspond to this study result.

Subject with bilateral endometriosis cyst have lower rate to get pregnant 1 year after laparoscopy (27.03%) compared to subject with unilateral endometriosis cyst (48.15%). Eventhough, association of bilaterality endometriosis cyst with pregnancy rate is statistically not significant (p value = 0.082).

Moreover, association between previous pregnancy and non patent in one tube with pregnancy rate is statistically not significant (p value = 0.153 and 0.073, respectively), although there is a difference in percentage. Pregnancy rate after laparoscopy in subject with primary infertility is 22.22%, while subject with secondary infertility is 41.30%. Pregnancy rate after laparoscopy in subject with non patent one of tube is 58.33% and subject with both tubes patent is 30.77%.

In this study, pregnancy outcomes in infertility patient with endometriosis cyst after laparoscopy cystectomy are term pregnancy (69.56%), preterm birth (17.39%), miscarriages (4.34%), IUFD (4.34%), and ectopic pregnancy (4.34%). Nesbitt-Hawess et al (2015) reported pregnancy outcomes after laparoscopy in infertility women with endometriosis are 64% term pregnancy, 8% preterm birth, 23% miscarriage, and there is no ectopic pregnancy.[14]

Pregnancy outcomes perhaps did not have association with endometriosis directly due to a lot of factors during pregancy that can affect outcome, such as anemia, malnourished, and infection.[15] Ectopic pregnancy in this study occurs in subject with one of tube non patent, grade r-AFS III, and age ≤ 35 years old. Miscarriages occurs in subject with both tubes patent, grade r-AFS IV, and age 36-39 years old.

CONCLUSIONS

This study find that pregnancy rate within firts year after laparoscopic cystectomy in infertility patient with endometriosis cyst is 35.94%. Factors like age, infertility interval, r-AFS grading have association with pregnancy rate after laparoscopy. The lower age, infertility interval, and r-AFS grading the higher pregnancy rate. Pregnancy outcome in term pregnancy is 69.56%.

RECOMMENDATIONS

Further multicenters study with larger sample size are required to represent the population of endometriotic patients and get prognostic value from predisposing factors, this a predictive scoring system of laparoscopic procedure for infertility patient with endometriosis could be obtained.

REFERENCES

1. Hoffman BL, Williams JW. Williams gynecology. 2nd ed. New York: McGraw-Hill Medical; 2011: 869-75.
2. Speroff L, Fritz AM. Endometriosis. Clinical Gynecologic Endocrinology and Fertility 8 ed. Philadelphia: Lippincott Williams and Wilkins; 2011: 1221-48.
3. Waller KG, Lindsay P, Curtis P, Shaw RW. The prevalence of endometriosis in women with infertile partners. Eur J Obstet Gynecol Reprod Biol. 1993; 48(2): 135-9.
4. Garrido N, Pellicer A, Remohi J, Simon C. Uterine and ovarian function in endometriosis. Semin Reprod Med. 2003; 21: 183-92.
5. Trinder J, Cahill DJ. Endometriosis and infertility: the debate continues. Hum Fertil (Camb). 2002; 5: S21-7.
6. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005: 1334-45.
7. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005; 20(10): 2698-704.
8. Meyer WR, Castelbaum AJ, Somkuti S, Sagoskin AW, Doyle M, Harris JE, et al. Hydrosalpinges adversely affect markers of endometrial receptivity. Hum Reprod Update. 1997; 12: 1393-8.
9. Quaas A, Dokras A. Diagnosis and Treatment of Unexplained Infertility. Reviews in Obstet Gynecol. 2008; 1(2): 69-76.
10. Jacobson TZ, Duffy J, Barlow DH, Farquhar C, Koninckx PR, Olive D. Laparoscopic surgery for subfertility associated with endometriosis. The Cochrane Library. 2014.
11. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med. 1997; 337(4): 217-22.
12. Lee HJ, Lee JE, Ku SY, Kim SH, Kim JG, Moon SY, et al. Natural conception rate following laparoscopic surgery in infertile women with endometriosis. Clin Exp Reprod Med. 2013; 40(1): 29-32.
13. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010; 94: 1609-15.
14. Nesbitt-Hawes EM, Campbell N, Maley PE, Won H, Hooshmand D, Henry A, et al. The Surgical Treatment of Severe Endometriosis Positively Affects the Chance of Natural or Assisted Pregnancy Postoperatively. Biomed Res Int. 2015; 2015: 438790.
15. Cunningham FG, Williams JW. Williams obstetrics. 23rd ed. New York: McGraw-Hill Medical; 2010. xv, 1385-92.

Research Article

Relationship between Knowledge, Attitude and Behavior of Postnatal Woman Toward Participation in Permanent Contraception

Hubungan Pengetahuan, Sikap dan Perilaku Ibu Pascasalin terhadap Partisipasi Kontrasepsi Mantap Perempuan

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Abstract

Objective: To investigate the association between knowledge, attitude, and behavior towards participation in permanent contraception and describe factors that could affect participation of permanent contraception in women in RSMH Palembang.

Methods: This case control study was conducted at the Department of Obstetrics and Gynecology, Dr. Mohammad Hoesin Hospital/ Faculty of Medicine, Universitas Sriwijaya, Palembang, during the period of June 2016 to December 2016. Sample of the cases group was woman who agreed to use permanent contraception while control sample was women who refuse to use permanent contraception. Data were collected using a questionnaire. Statistical analysis was performed using SPSS.

Results: There was a significant association between attitude, behavior, husband support, and disease complications with participation of permanent contraception. Factors that influenced participation of permanent contraception in woman in RSMH Palembang include husband support and behavior.

Conclusion: Factors that influence the participation of women in RSMH safe contraception Palembang include support for her husband and behavior.

[Indones J Obstet Gynecol 2018; 6-1: 39-44]

Keywords: family planning, participation, permanent contraception

Abstrak

***Tujuan**: Mengetahui hubungan antara pengetahuan, sikap dan perilaku terhadap partisipasi kontrasepsi mantap dan mendeskripsikan faktor-faktor yang dapat mempengaruhi partisipasi kontrasepsi mantap perempuan di RSMH Palembang.*

***Metode**: Penelitian kasus kontrol ini dilakukan di Departemen Obstetri dan Ginekologi di Rumah Sakit Dr. Mohammad Hoesin/ Fakultas Kedokteran Universitas Sriwijaya Palembang sejak Juni 2016 hingga Desember 2016. Sampel kasus adalah perempuan yang setuju menggunakan kontrasepsi mantap sedangkan sampel kontrol adalah perempuan yang menolak kontrasepsi mantap. Data dikumpulkan dengan menggunakan kuesioner. Analisis statistik dilakukan dengan program SPSS.*

***Hasil**: Ada hubungan bermakna antara sikap, perilaku, dukungan suami, usia, dan penyakit penyulit dengan partisipasi kontrasepsi mantap. Faktor-faktor yang mempengaruhi partisipasi kontrasepsi mantap perempuan di RSMH Palembang antara lain dukungan suami dan perilaku.*

***Kesimpulan**: Faktor-faktor yang mempengaruhi partisipasi kontrasepsi mantap perempuan di RSMH Palembang antara lain dukungan suami dan perilaku.*

[Maj Obstet Ginekol Indones 2018; 6-1: 39-44]

***Kata kunci**: keluarga berencana, kontrasepsi mantap, partisipasi*

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INTRODUCTION

Family planning is a program aiming to help married couples avoiding unwanted births, getting wanted pregnancy, setting interval between pregnancies and birth, and determining the number of children in a family.[1,2]

According to the 2010 Population Census, the population of Indonesia is 237.556.363 peoples. Population Growth Rate during period of 2000-2010 is 1.49%, this was higher than growth rate in 1990-2000 which was 1.45%. The total area of Indonesia is estimated to be 1,910,931 km^2, whereas the population density is 124 km^2. Based on these data, Indonesia is the world's fourth most populous country.[3]

New paradigm of National Family Planning Program has changed its vision from "Norm of Small, Happy and Prosperous Family" (NKKBS) became a vision to actualize "Quality Family 2015". Quality family is a prosperous, healthy, and independent family with ideal number of children,

forward-looking, responsible, harmonious and devoted to God Almighty.[2]

To achieve the objectives of National Medium Term Development Plan (RPJMN 2010-2014) and changing of strategic environment and to achieve target of Millennium Development Goals (MDGs) which is embody access to reproductive health by 2015, then provision of quality Long Term Contraception Method (LTCM) is expected to increase number LTCM participation by couples of childbearing age at all stages of the family, and hopefully national Total Fertility Rate (TFR) will decline.[4,5]

Use of LTCM in Indonesia is still relatively low. Based on Indonesian Demographic Health Survey, participant of LTCM decreased from 14.6% (2002/2003) to 10.9% (2007). Participation of Intra Uterine Device (IUDs) tend to decrease from 8.1% to 6.2% (IDHS 2002/2003) and fell further to just 4.9%. Subdermal contraception (AKBK) also tend to decline more than 50 percent, from 6 percent to 2.8%. Although Woman Operative Methods (MOW) had increased by 3.7%, participation rate dropped to 3%. Man Operative Method (MOP) had stagnated at 0.4% and participation rate dropped to 0.2%. Pattern of contraceptive use in Indonesia is still dominated by hormonal and short term contraception.[5-7]

Decision to participate in family planning is influenced by many factors such as knowledge, attitude and behavior towards contraception as well as other factors such as family support, environment, religion and customs regulations. To increase the use of MOW as a contraceptive method of choice, it is necessary to know factors that influence the decision making of contraceptive use in woman.[1,2]

METHODS

This was an observational case-control study. The study was conducted at Obstetrics and Gynecology Department of Dr. Mohammad Hoesin Hospital/ Faculty of Medicine, Universitas Sriwijaya, since June 2016 to December 2016. Case sample was postnatal women who have agreed and use permanent contraception in RSMH Palembang, while control group was postnatal women who refuse to use permanent contraception. Patients who were obese or overweight, have pelvic abnormalities such as adhesions and infections, or have severe illness (cardiorespiratory problems) were excluded from analysis.

Patients who met inclusion criteria were given an explanation about the study and signed informed consent. Then patients were asked to fill out questionnaires that have been provided.

Distribution and frequency of data presented in the form of textural and tables. Data were analyzed using Chi-square test or Fisher and logistic regression analysis. Data is processed by SPSS (Statistical Package for the Social Science) for Windows.

RESULTS

Table 1. Characteristics of Study Subjects

Variables	Persistent Contraception			
	Yes		No	
	n	%	n	%
Age				
> 35 yo	32	58.2	20	36.4
≤ 35 yo	23	41.8	35	63.6
Number of children				
> 3	27	49.1	24	43.6
≤ 3	28	50.9	31	56.4
Education				
Uneducated	6	10.9	3	5.5
Elementary school	18	32.7	15	27.3
Junior high school	12	21.8	11	20.0
Senior high school	15	27.3	19	34.5
University	4	7.3	7	12.7
Occupation				
House wife	48	87.3	42	76.4
Civil servant	1	1.8	3	5.5
Trader	3	5.5	5	9.1
Farmer	1	1.8	1	1.8
Private company	2	3.6	4	7.3
Religion				
Non Muslim	0	0	1	1.8
Muslim	55	100	54	98.2
Social Economic Status				
≤ UMR	42	76.4	36	65.5
> UMR	13	23.6	19	34.5

Assurance				
Askin	11	20.0	7	12.7
BPJS	20	36.4	17	30.9
Jamkesmas	1	1.8	2	3.6
Jamsoskes	14	25.5	22	40
KIS	8	14.5	6	10.9
None	1	1.8	1	1.8
Tribe				
Sumatera	38	69.1	45	81.8
Non Sumatera	17	30.9	10	18.2
Disease complication				
Yes	30	54.5	17	30.9
No	25	45.5	38	69.1

During study period we included 110 samples consisted of 55 postnatal women who agreed and used permanent contraception in RSMH Palembang and 55 postnatal mother who refused to use permanent contraception. Patient characteristics were shown in Table 1.

We found a significant association between age and disease complications with participation of permanent contraception. Age >35 years and disease complication was 2,435 times and 2,682 times respectively more possible to participate in permanent contraception (p <0.05). Number of children, education and socio-economic status was not significantly associated with participation of permanent contraception (Table 1).

Based on recapitulation of responses to questionnaires about knowledge (Gutzman Scale), attitude (Likert Scale) and behavior (Gutzman Scale) we get a category of knowledge, attitudes and behavior of respondents as shown in Table 3.

Based on logistic regression test (Table 5), it can be concluded that husband's support significantly influence participation of permanent contraception (OR = 188.709, p value = 0.000). In addition, behavior also significantly affects participation of permanent contraception (OR = 10.260, p value = 0.023). Knowledge (OR = 0.380, p value = 0.223) and behavior (OR = 4.196, p value = 0.497) did not affect participation of permanent contraception.

Table 2. Analysis of Correlation between Subjects Characteristics and Participation of Permanent Methods

Characteristics	Participation of permanent methods		Total	OR* (CI 95%)	p value*
	Yes	No			
Age					
> 35 yo	32	20	52	**2.435**	**0.036**
≤ 35 yo	23	35	58		
Number of children					
> 3	27	24	51	**1.246**	**0.702**
≤ 3	28	31	59		
Education					
Low	36	29	65	**1.699**	**0.245**
High	19	26	45		
Social Economic					
≤ UMR	42	36	78	**1.705**	**0.294**
> UMR	13	19	32		
Disease complication					
Yes	30	17	47	**2.682**	**0.021**
No	25	38	63		
Total	55	55	110		

**Uji Chi Square, p value = 0.05*

Table 3. Characteristics Analysis of Factors Affecting Participation of Permanent Contraception

Variables	Participation of permanent contraception			
	Yes		No	
	n	%	n	%
Knowledge				
Good	47	85.5	46	84.5
Bad	8	14.5	9	15.5
Attitude				
Good	48	85.5	6	10.9
Bad	7	14.5	49	89.1
Behaviour				
Good	51	92.7	18	32.7
Bad	4	7.3	37	67.3
Husband Support				
Yes	54	98.2	4	7.3
No	1	1.8	51	92.7

Table 4. Factors Affecting Participation of Permanent Contraception

Variables	Unadjusted*		Adjusted**	
	OR	p value	OR	p value
Support	688.5	0.000	188.709	**0.000**
Behaviour	56.00	0.000	10.260	0.023
Attitude	26.208	0.000	4.196	0.223
Knowledge	1.149	1.000	0.380	0.497

** Logistics regression, p value = 0.05*

DISCUSSION

Permanent contraception is any action on woman's fallopian tubes or man's vas deferens which resulted on infertility, based on request of husband or wife.[1,2,8]

Age of most women in case group was >35 years and there is a relationship between age and participation of safe contraception (OR = 2.435; p = 0.036). Results of this study are not much different from study by Sekar Mutiara in 2010. They found that most women who agreed to use permanent methods was >30 years old, but it was only a descriptive study without assessing the relationship between age and the participation of permanent contraception. This result was in contrast to research by Herlinawati et al in 2012, age of women who choose permanent contraception mostly was 20-35 years and they did not found relationship between age and selection of permanent contraception (OR = 2.051; p = 0.152). Type of contraception should be adapted to stage of reproductive period. Age >35 years is an old reproductive period (36-45 years) and an end of fertility period, so at the age of >35 years women are more likely to approve permanent contraception.[6,9-11]

Women who agreed (50.9%) or rejected to (56.4%) participated in permanent contraception mostly had ≤3 children, the proportion was lower in rejected group. There is no relationship between number of children with participation of permanent contraception (OR = 1.246; p = 0.702). These results was in contract with study by Herlinawati et al (2012) which found that woman who approve or reject permanent contraception mostly had >3 children with higher proportions in woman who agree to participate in permanent contraception (OR = 13.254; p = 0.001). Difference in this study may be due to the proportion of number of children > 3 and ≤3 in women who agree to use permanent contraception was almost the same.[9,10,11]

Most subjects in both groups have incomes ≤UMR (76.4% in case and 65.5% in control group). There is no correlation between economic status with participation of permanent contraception (OR = 1.705; p = 0.294). Results of this study were not much different from study by Sekar Mutiara in 2010. Influence of socio-economic status in family planning is correlated with opportunity or ability to obtain family planning facilities.[6,12-14]

Majority of women who choose contraception have low education (64.46%). There is no relationship between education and participation of permanent contraception (OR = 1.699; p = 0.245). These results were in contrast to studies conducted by Ismail and Sisca in 2012 in Karangampel l village Kidul District Indramayu. They found that women who agree to use permanent contraception had higher education (73.68%) and they found an association between level of education and selection of permanent contraception (OR = 2.520; p = 0.020). A similar result was reported by Herlinawati et al (2012). Different result found in this study may be due to low knowledge of permanent contraception in both case and control group.[13,15,16]

Most subjects in this study mostly had disease complications. There was a relationship between disease complications with participation of permanent contraception. Women with disease complications 2,682 times more likely to participate in permanent contraception (OR = 2.682; p = 0.021). These results are in contrast to studies conducted by Sekar which found that most woman (86%) who had disease history refused to participate in permanent contraception. Results of this study supported by Pratama (2005) which found a significant association between disease history with use of permanent contraception (OR = 11.3; p = 0.014; 95% CI: 1.360 to 94.248). Hormonal contraceptive use is contraindicated in patients with disease complications so they prefer to use permanent contraception.

We did not find any relationship between knowledge and participation of permanent contraception. Results of this study were not much different from study by Herlinawati et al (2012) who also found no correlation between knowledge with participation of permanent contraception in Dr. Pirngadi hospitals (OR = 1.850; p = 0.397). Results of this study was different from results of study conducted by Ismail and Sisca in 2012 in Karang-ampel village Kidul District Indramayu. They found that women with good knowledge 2.474 times more likely to choose permanent contraception. Woman who has good knowledge may refuse permanent contraception due to other factors such as husband support or a number of children.

There is a significant relationship between attitude with participation of permanent contra-ception. This result was consistent with study by Herlinawati et al (2012) which show a significant association between attitudes and participation of permanent contraception in Dr. Pirngadi hospitals (OR = 8.255; p = 0.016). In this study behavior was 56 times more likely to affect participation of permanent contraception.

Logistic regression analysis showed that husband's support was the most important factors that affect participation of permanent contra-ception. Husband support was 188.7 times more likely to affect participation of permanent contra-ception. Results of this study is supported by study by Herlinawati et al (2012) which showed a significant relationship between family support with participation of permanent contraception in Dr. Pirngadi hospitals (OR = 12.016; p = 0.001).

Responsibility of reproductive health care, especially in the use of contraceptives predominantly done by woman, although in the decision making process men are involved, men are tend to be passive.[17,18]

Husband's participation in family planning programs and reproductive health care is an important factor. This participation will be achieved if various information relating to it always available. We all know that low participation of men/husbands in family planning and reproductive health is caused by limited information, especially for couples.[6,17,18]

Inability to communicate in decision making process placing housewife in low bargaining position, so that their needs and desires is difficult to fulfilled. Decisions are more likely dominated by interests of her husband; even if the decision involves issues relating to women's live such as reproductive health problem.[19]

In this study, husband's support was an important factor. 98.2% woman who participate in permanent contraception reported that they received husband's support, meanwhile in woman who rejected to use permanent contraception 92.7% did not received husband's support.

CONCLUSION

There was a significant relationship between attitude, behavior, age and disease complication with participation of permanent contraception. Factors that influence the participation of women in RSMH safe contraception Palembang include support for her husband and behavior.

REFERENCES

1. Irianto K. Pelayanan Keluarga Berencana Dua Anak Cukup. Bandung: Alfabeta; 2014: 8-10.
2. Yuhedi LT, Kurniawati T. Buku Ajar Kependudukan dan Pelayanan Keluarga Berencana. Jakarta: EGC; 2011: 21-6.
3. Profil Hasil Pendataan Keluarga Tahun 2011. Jakarta: Badan Kependudukan dan Keluarga Berencana Nasional Direktorat Pelaporan dan Statistik; 2011: 14-20.
4. Setyorini A. Kesehatan Reproduksi dan Pelayanan Keluarga Berencana. Bogor: In Media; 2014: 17-22.
5. Asih L, Oesman H. Faktor yang Mempengaruhi Pemakaian Kontrasepsi Jangka Panjang. Jakarta: Puslitbang KB dan Kesehatan Reproduksi BKKBN; 2009: 33-8.
6. Nasution SL. Faktor - Faktor yang Mempengaruhi Penggunaan MKJP di Enam Wilayah Indonesia. Jakarta: Puslitbang KB dan Keluarga Sejahtera BKKBN; 2011: 55-62.

7. Alemayehu M, Belachew T, Tilahun T. Factors associated with utilization of long acting and permanent contraceptive methods among married women of reproductive age in Mekelle town, Tigray region, north Ethiopia. BMC pregnancy and childbirth. 2012; 12: 1-9.
8. Sulistyawati A. Pelayanan Keluarga Berencana, Jakarta: Salemba Medika; 2011: 26-8.
9. Priyoto. Teori Sikap dan Perilaku dalam Kesehatan. Yogyakarta: Nuha Medika. 20114-22.
10. Green LW, Iverson DC. School Health Education. Ann. Rev. Public Health. 1982; 3: 321-38.
11. Grady T, Cynthia D. Does a history of unintended pregnancy lessen the likelihood of desire for sterilization reversal? J Women's Health, 2013; 22(6): 501-6.
12. Eliminating forced, coercive and otherwise involuntary sterilization: an interagency statement, OHCHR, UN Women, UNAIDS, UNDP, UNFPA, UNICEF and WHO. 2014: 3-8.
13. The Respond Project. Synthesis of Female Sterilization Literature Review. USAID. 2013: 1-7.
14. Borrero R, Sonya D. Racial variation in tubal sterilization rates: role of patient-level factors. Fertil Steril, 2011; 95(1): 17-22.
15. Factors Influencing Sterilization Use and Outcomes from Contraceptive Sterilization: Global Issues and Trends. Engender Health. 2002: 107-21
16. Azwar S. Sikap Manusia Teori dan Pengukurannya, Ed 2, Yogyakarta, Pustaka Pelajar. 1995: 10-6.
17. Lawrence RE. Factors influencing physicians advice about female sterilization in USA: a national survey. Hum Reprod. 2011; 26(1): 106-11.
18. Machado, Katia MM, Bernarda A, Ludermir, Da Costa AM. Changes in family structure and regret following tubal sterilization. Cad. Saúde Pública. 2005; 26(1): 1768-77.
19. Reichwein J, Vaid W. What obstacles do rural Indian women face when attempting to end an unwanted pregnancy? Research Brief: Marie Stopes Int. 2013; 001: 1-6.

Research Article

A Comparative Study of Nomegestrol Acetate and a Combination of Ethinylestradiol and Levonorgestrel for Delaying Menstruation among Umrah Pilgrims

Suatu Studi Komparatif Mengenai Nomegestrol Asetat dengan Kombinasi Etinilestradiol dan Levonorgestrel untuk Menunda Haid pada Jamaah Umrah

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Abstract

Objective: To compare the effectiveness efficacy of nomegestrol acetate with and combination of ethinylestradiol and levonorgestrel as a regimen for delaying menstruation in Umrah pilgrims in Palembang city.

Methods: This single-blind randomized controlled trial was conducted in Hajj and Umrah Guidance Group in Palembang city during December 2016 to January 2017. Population of this study was 30 women who meet the inclusion and exclusion criteria. Frequency and distribution of data was described in a table. Effectiveness and the side effects treatment between the two groups were analyzed with Chi Square test. Data was were analyzed using SPSS version 18.0.

Results: There were no differences in age, education, occupation, parity, body weight, height and contraceptive history between two both groups (all p values > 0.05). Statistical analysis showed there was no difference in spotting between nomegestrol acetate 5 mg or a combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol in Umrah pilgrims (p = 1.000). Other side effects such as (dizziness, depression, breast tenderness, heavy limbs, nauseam and vomiting) between the two groups could not be analyzed because all subjects did not experience any other side effects.

Conclusion: There is no difference in effectiveness between nomegestrol acetate 5 mg or combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol as a regimen for delaying menses in Umrah pilgrims in Palembang city.

[Indones J Obstet Gynecol 2018; 6-1: 45-49]

Keywords: delay menstruation, ethinylestradiol, levonorgestrel, nomegestrol, side effects, spotting, umrah

Abstrak

***Tujuan**: Mengetahui perbandingan efektivitas nomegestrol asetat dengan kombinasi etinilestradiol dan levonorgestrel sebagai regimen penunda haid pada jamaah umrah di Kota Palembang.*

***Metode**: Uji klinis acak berpembanding secara buta tunggal dilakukan di Kelompok Bimbingan Ibadah Haji Dan Umrah di kota Palembang pada periode bulan Desember 2016 sampai Januari 2017. Populasi penelitian ini sebanyak 30 wanita yang memenuhi kriteria inklusi dan eksklusi. Frekuensi dan distribusi data dijelaskan dalam bentuk tabel. Efektivitas perlakuan dan efek samping perlakuan antar kedua kelompok dianalisa dengan Uji Chi Square. Analisis data menggunakan SPSS versi 18.0.*

***Hasil**: Tidak terdapat perbedaan usia, pendidikan, pekerjaan, paritas, berat badan, tinggi badan dan riwayat kontrasepsi antara kedua kelompok. Tidak terdapat perbedaan efek samping spotting antara perlakuan nomegestrol asetat 5 mg maupun kombinasi levonorgestrel 150 mcg dan etinilestradiol 30 mcg pada jamaah umrah (p = 1,000). Efek samping lain (pusing, depresi, nyeri payudara, tungkai berat, mual dan muntah) antara kedua kelompok tidak dapat dianalisis karena seluruh subjek tidak mengalami efek samping lain.*

***Kesimpulan**: Tidak terdapat perbedaan efektivitas antara nomegestrol asetat 5 mg maupun kombinasi levonorgestrel 150 mcg dan etinilestradiol 30 mcg sebagai regimen penunda haid pada jamaah umrah di Kota Palembang.*

[Maj Obstet Ginekol Indones 2018; 6-1: 45-49]

***Kata kunci**: efek samping, etinilestradiol, levonorgestrel, nomegestrol, penundaan haid, spotting*

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INTRODUCTION

Menstruation occurs periodically in all healthy women who have with healthy reproductive organs. Menstrual cycle is often a problem for women (for example, when running Hajj or Umrah) because Islamic law forbids women who are menstruating to do prayer. Hajj and Umrah is a prayer that is performed at a given time and requires a certain amount of time and cannot be implemented at the time of menstruation. During

menstruation, there are some prayer that should not be done, including: thawaf, praying, reading Quran, fasting and having a moment of silence in mosque.[1-3]

Advancement in the field of hormonal therapy has allowed us to regulate time of menstruation as desired, either to advance or delay menstruation using hormonal preparations such as progesterone, combined oral contraceptive pill, and GnRH agonists.[4]

The mechanism of menstrual regulation using hormonal preparations is by suppressing production of endogenous estrogen and progesterone (ovarian) by providing a combination of exogenous hormones that suppress ovulation. Some regimens that can be provided to regulate menstrual cycle are progestin (progesterone or testosterone derivative), combination oral contraceptive (combination of estrogen and progestin), and gonadotropin releasing hormone agonist (GnRH). These preparations do not result in permanent infertility and menstrual cycle will back to normal after menstrual cycle regimen is stopped.[2-5]

Regulation of menstrual cycle, either to advance or delay menstruation was done to shift menstruation into some time before the pilgrimage begins or after the pilgrimage is completed. To reach that goal, we have to choose simple, rational, effective, efficient, and in expensive regiments.[6]

Westhoff C et al. reported the use of nomegestrol acetate and 17β-estradiol, they found that 67.1% of women reported on time bleeding schedule and 85% reported on time bleeding until 12 cycles. In 2011 Australian State Health Department reported that 83.6% of women who use nomegestrol acetate did not report bleeding and spotting during the observation for 12 cycles.[7-9]

In this study, we used acetate nomegestrol preparations (Lutenyl) and combination of ethinylestradiol and levonorgestrel (Microgynon). Both drugs are used because both are widely circulated, easy to obtain, have adequate contraceptive effect, and a relatively affordable price.

Providing reproductive health services, including regulating menstruation for woman who will do Hajj and Umrah is one of obstetrician resposibilities. Data regarding efficacy and side effects of regiments used to regulate menstruation during Umroh had not available. For that this study is aimed reason, we interested to compare effectiveness of nomegestrol acetate and combination of levonorgestrel and ethinylestradiol as a regimen for delaying menses in Umrah pilgrims in Palembang city.

METHODS

This was a single-blind randomized controlled trial. Study subjects are were blinded from regiments allocation. This study was conducted in Hajj and Umrah Guidance Group in Palembang from December 2016 until to 2017.

The population in this study were all Umrah pilgrims women in Hajj and Umrah Group Guidance (KBIH/U) in Palembang during 2016-2017.

Inclusion criteria was were Umrah pilgrims, were in the reproductive age (20-45 years), still having periods, not pregnant, not in infertility therapy, and willing to participate in this study proved by signing informed consent.

Exclusion criteria were previous history of removal of the uterus or both ovaries, having diseases in kidney, liver, or heart, history of embolism, postpartum <4 weeks, history of DVT (deep vein thrombosis), hypertension, migraine with aura, cervical cancer, endometrial cancer, breast cancer, taking drugs that interact with hormonal preparations, and refused to participate in this study.

Women who met the inclusion criteria were given a serial number then they were asked to sign informed consent. We did anamnesis history taking, physical examination and gave an explanation about this study to study subject. Subjects were given nomegestrol acetate 5 mg (Lutenyl) 1 time a day orally or combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol (Microgynon) 1 time a day orally. Drugs taken on day 5 (maximum in day 14) of menstrual cycle every day until Umrah was completed. Subjects were given a bleeding and side effects control card and it must be filled during drugs comsumption.

The effectiveness and side effects of the treatment between two groups were analyzed using Chi Square. Data was were analyzed using SPSS version 18.0. Frequency and data distribution were described in table 5.

RESULTS

Demographic characteristics of study subjects are presented in Table 1. We did not find any differences in age, education, employment, weight and height, parity, marital status and history of contraception among group receiving 5 mg of nomegestrol acetate and combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol. We can conclude that our study results were not influenced by demographic factors and those two groups was comparable.

From statistical analysis, we did not found significant difference in incidence of spotting (mid periode bleeding) between among groups who received nomegestrol acetate 5 mg and combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol (p = 1.000) (Table 2).

All study subjects either in nomegestrol acetate 5 mg group and combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol did not reported other side effects (such as dizziness, depression, breast tenderness, heavy limbs, nausea and vomiting), for this reason we could not perform statistical analysis.

Table 1. Characteristics of Study Subjects

Characteristics	Study Groups		p-value
	Nomegestrol asetate 5 mg	Levonorgestrel 150 mcg + Etinylestradiol 30 mcg	
Age (years), mean ± SD	33.13 ± 9.67	36.33 ± 7.96	0.372*
Education			
SD	0	0	0.183**
SMP	1	2	
SMA	5	9	
University	9	4	
Employment			
Housewife	8	11	0.405**
Private company	2	1	
Civil servant	2	0	
Student	3	2	
Midwife	0	1	
Marital status			
Married	11	13	0.651**
Not married	4	2	
Weight (kg), mean ± SD	56.8 ± 8.00	58.6 ± 6.02	0.277*
Height (cm), mean ± SD	154.40 ± 5.64	154.13 ± 4.21	0.752*
Parity, mean ± SD	2.067 ± 1.87	2.533 ± 1.55	0.463***
Contraceptive			
history	10	8	0.719*
No contraception	1	2	
Injectable	3	2	
IUD	1	2	
Pills	0	1	
Implant			

** Mann_Whitney, -p = 0.05*
*** Chi Square (Pearson, Fisher exact test), p = 0.05*
**** Independent T Test, p = 0.05*

Table 2. Comparison of Spotting after Study Intervention

Characteristics	Nomegestrol acetate 5 mg	Levonorgestrel 150 mcg + Etinylestradiol 30 mcg	Total	p*	
Spotting (+)		2	1	3	1.000
Spotting (-)		13	14	27	
Total	15	15	15	30	

**Fisher exact test, p = 0.05*

DISCUSSION

Menstruation is a natural process for all normal women and a sign of fertility. Normal menstrual cycle is about 28 days but can be forward or backward and ranged from 22 days to 35 days with an average volume of blood about 130 ml. Menstruation is often a problem for women who will do Hajj or Umrah because Islamic law forbids menstruating women to worship God. Solutions to address this problem is by regulating menstrual cycle, including forward or delay menstruation using hormonal preparations such as progesterone, combined oral contraceptive pill, and agonists GnRH.[1-4]

Preparations for menstrual regulation should be simple, rational, effective, efficient, and inexpensive. Delaying menstruation can be done using combined contraceptive pill (estrogen and progestin) or using progesterone only pills. In this study we used single dose of hormonal preparations (nomegestrol acetate 5 mg under the brand mixes Lutenyl) and combinations dose (levonorgestrel 150 mcg and 30 mcg ethinylestradiol the trademark Microgynon).[6,7]

Statistical analysis showed that there were no differences in age, education level, employment, marital status, weight, height, parity and contraceptive history between two groups so that both groups were comparable.

The most common side effects occurs after nomegestrol acetate administration are bleeding (spotting), amenorrhea, edema, allergic. But however, in this study, bleeding (spotting) only occurs by 13.3%. Incidence of spotting in combination pill was quite low (6.7%).[7-10]

In this study we found only three subjects that experienced spotting, two from nomegestrol acetate 5 mg group and 1 from combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol group. Statistic analysis showed that there was no difference in spotting between nomegestrol acetate 5 mg group or combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol group. We did not found other adverse effects in both groups. From those results it can be concluded that nomegestrol acetate 5 mg group and 1 from combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol have the same effectiveness as regimen to delay menstruation and has no adverse side effects.

Other side effects that often occur after nomegestrol acetate 5 mg or combination of levonorgestrel 150 mcg and 30 mcg ethinylestradiol administration were nausea, abdominal pain, weight gain, headaches, distressed and breast tenderness. These side effects can occur in ≥ 1% of users, but in this study those side effects were not found.[8,11,12]

Nomegestrol acetate is a potent oral progestogens that have has a good tolerability profile and neutral metabolic characteristics. Nomegestrol acetate, or 19-nomegestrol acetate, is a hormonal contraceptive that is selective for receptor binding progesteron and have smaller power against other steroid receptors such as androgen receptor, estrogen, glucocorticoid and mineralocorticoid receptors. As a result, this hormone has no androgenic, estrogenic, glucocorticoid or mineralocorticoid effect. Nomegestrol acetate has been used to treat gynecological disorders (menstrual disorders, dysmenorrhea, and premenstrual syndrome) and as a component in hormone replacement therapy combined with estradiol to reduce symptoms of menopause. Nomegestrol acetate has a good effect on lipid profile, and has no bad effect on glucose metabolism. Nomegestrol acetate showed no proliferative activity in normal breast or women who have malignancy, and do not give a bad effect on bone formation.[7-10]

The combination of estradiol and levonorgestrel is commonly used as an oral contraceptive. Combination pill is effective to inhibit activity of hypothalamo-pituitary-ovarial axis. Menstruation delay can also achieve with combined contraceptive pill (estrogen and progestin). Use of combination hormone is usually more effective to suppress activity of hypothalamo-pituitary-ovarian axis than single hormone but have greater side effects. This was contrast with results of this study which shows that incidence of spotting or other adverse effects between single hormone or combination preparation was not different.[11,12]

CONCLUSION

There is no difference in effectiveness between nomegestrol acetate 5 mg or combination of levonorgestrel 150 mcg and 30 mcg ethinyl-estradiol as a regimen for delaying menses menstruation in Umrah pilgrims in Palembang city.

RECOMMENDATION

Based on the study results, drugs choice should depend on the preferences of each woman.

REFERENCES

1. Astarto NW, Djuwantono D, Tjahyadi D. Menunda Haid dan Mengatasi Masalahnya ketika Beribadah Haji dan Umrah. Step by Step Penanganan Kelainan Endokrinologi reproduksi dan Fertilitas dalam Praktik sehari-hari. CV Sagung Seto. Jakarta. 2012: 5-20.
2. Dahlan S, Sarjana. Kontroversi Pil Tunda Haid Selama Haji. 2007. Available at: http://www.wordpress.com/2014.html
3. Rajuddin. Ibadah Haji dan Upaya Mengatur Siklus Haid. Majalah Ilmiah Ukhuwah, Universitas Al Wasliyah, Medan. 2009; 4(2): 169-79.
4. Baziad A. Penggunaan Progesteron dalam Pengobatan. Ilmu Kandungan. PT Bina Pustaka Sarwono Prawirohardjo. Jakarta. 2009: 648.
5. Caitlin WH, Ellen SR. Menstrual Manipulation: Options for Supressing The Cycle. Cleveland Clin J Med. 2010; 27: 445-51.
6. Frankovich RJ, Lebrun CM. Menstrual Cycle, Contraception and Perfomance. Clin Sport Med. 2000; 19: 251-71.
7. Westhoff C Kaunitz AM, Korver T, Sommer W, et al. Efficacy, Safety, and Tolerability of a Monophasic Oral Contraceptive Containing Nomegestrol Acetate and 17β-Estradiol. A Randomized Controlled Trial. Obstet Gynecol 2012; 119: 989-99.
8. Department of Health and Ageing, Australian Government. Australian Public Assessment Report for Nomegestrol acetate/oestradiol. 2011: 1-101.
9. Conyngham RB. Noretisterone in menorrhagia. New Zealand Med J 64: 697-701.
10. Greenblat RB, Junck EC. Delay of menstruation with norethindrone, an orally given progestational compound. JAMA. 1958; 166(12): 1461-3.
11. Miller L, Hughes JP. Continous Combination on contraceptive pils to eliminate withdrawal bleeding. A randomized trial. Obstet Gynecol. 2003; 101: 653-66.
12. Sulak P, Kueh T, Ortiz M, Shull BL. Acceptance of altering the standard 21 day 17 day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. Am J Obstet Gynecol. 2002; 186: 1142-9.

Research Article

Obstetric Risk Factors and Anal Incontinence among Women with Previous History of Vaginal Delivery

Faktor Risiko Obstetri dan Kejadian Inkontinensia Ani pada Ibu Riwayat Persalinan Pervaginam

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Abstract

Objective: To investigate the obstetric risk factors of the anal incontinence in mothers with previous history of vaginal delivery.

Methods: The was a case-control study conducted in the Obstetrics and Gynecology Department of Dr.Wahidin Sudirohusodo Hospital, Faculty of Medicine, Universitas Hasanuddin, Makassar, during the period of February 2015 through January 2016. The research instruments were used to evaluate obstetric risk factors and the anal incontinence was the self-administered questionnaire and Fecal Incontinence Severity Index. The data were analyzed statistically using the Chi-square test with the significant value of p<0.05.

Results: A total of 300 subjects were recruited in this study. The research results indicated that the parity of ≥ 3, the assisted vaginal delivery history (vacuum extraction), and the prolong second stage of labor had a significant correlation with the anal incontinence with p value=0.026, OR (95% CI) = 1.8 (1.07-3.03), p=0.018 with OR (95% CI) =3.65 (1.2-10.7) and p=0.006 with OR (95% CI) = 2.9 (1.2-6.7).The history of episiotomy and the delivery of the baby ≥ 4000 gram had no correlation with the anal incontinence.

Conclusion: Parity, vacuum delivery and prolong second stage of labor have an association with anal incontinence among women who has history of vaginal delivery.

[Indones J Obstet Gynecol 2018; 6-1: 55-59]

Keywords: anal incontinence, obstetric risk factors, vaginal delivery

Abstrak

***Tujuan**: Untuk mengetahui beberapa faktor risiko obstetrik terhadap kejadian inkontinensia ani pada ibu riwayat persalinan pervaginam.*

***Metode**: Penelitian ini dilaksanakan di RS Wahidin Sudirohusodo dan jejaringnya di bagian obstetrik dan ginekologi yang dimulai pada tanggal 1 Februari 2015 sampai 31 Januari 2016. Metode yang digunakan adalah desain case-control dengan sampel berjumlah 300 orang. Instrumen yang digunakan untuk menilai faktor risiko obstetrik dan inkontinensia ani adalah self-adminnistered questionnaire dan fecal incontinence severity index. Data diolah dengan uji Chi-square dan tingkat signifikansi p<0,05.*

***Hasil**: Hasil penelitian ini menunjukkan bahwa paritas ≥3, riwayat persalinan vakum dan riwayat kala II lama berhubungan secara bermakna dengan kejadian inkontinensia ani di mana nilai p masing-masing 0,026 dengan OR (95%CI)= 1,8 (1,07-3,03), p= 0,018 dengan OR (95%CI)= 3,65 (1,2-10,7) dan p= 0,006 dengan OR (95%CI)= 2,91 (1,2-6,7). Riwayat episiotomi dan persalinan bayi ≥4000 gram tidak memiliki hubungan bermakna dengan inkontinensia ani.*

***Kesimpulan**: Paritas, persalinan vakum dan kala II lama berhubungan dengan kejadian inkontinensia ani pada perempuan riwayat persalinan pervaginam.*

[Maj Obstet Ginekol Indones 2018; 6-1: 55-59]

***Kata kunci**: faktor risiko obstetri, inkontinensia ani, persalinan pervaginam*

INTRODUCTION

Anal incontinence is a medical condition that affects quality of life. The prevalence of anal incontinence in the world varies from 0.4% to 20%.[1,2] Research in the United States got a prevalence for women and men as much as 2.6% in men aged 20-29 years and increased to 15.3% in men aged 70 years and over[3], and the French as much as 9.5% at age 50 -61 years.[1] In Indonesia, the prevalence of anal incontinence has not well documented. One of community study among aged over 60 years, the prevalence is 22.4%.[4]

Anal incontinence is defined as in voluntary loss of feces either liquid or solid.[5] Epidemiology consensus of anal incontinence define it as all incontinence of flatus, feces, liquid or solid that affect the quality of life of individuals.

The normal bowel movement is a combined process of somatoviseral response involving colo-recto-anal functions. The continence is a physiological complex function that requires coordination of brain, central nervous system, autonomic nervous system, the enteric; gastrointestinal tract and other biomechanical

capabilities including anal sphincter.[6] The ability to evacuate stool is influenced by several factors including the sphincter mechanism, detention reservoir, volume and consistency of stool, gut motility, the structural integrity of the pelvic wall, rectal sensation, colonic transit, and the sensation of anorectal reflex Incontinence occurs if one or more of these mechanalsmsis disrupted and other can not compensate.[7]

Numerous factors are associated with the occurrence of anal incontinence, such as age, obesity, obstetric trauma, chronic illnesses such as diabetes, rectal prolapse, colitis, rectal surgery, surgery for urinary incontinence and others. Independent risk factors that plays an important role is anal sphincter injury during childbirth.[8]

Anal incontinence is a symptom that initially assessed through a subjective assessment. One example of self-completion questionnaires, standardized, valid and reliable questionnaire is from the University of Auckland. This questionnaire was developed and validated in New Zealand, has obtained permission, using the Bristol Stool Form Scale, fecal incontinence severity index, and the index level of quality of life in anal incontinence.[9]

The obstetric risk factors of anal incontinence have been studied abroad, but in Indonesia, it still limited. Currently the research in community more than 60 years has been conducted in Bali. However study subjected to reproductive age has not been established. Therefore, the authors aims to identify the association of obstetric risk factors and anal incontinence in women with history of vaginal delivery. Identification of the risk factor will be highly beneficial for increasing women's quality of life.

METHODS

The was a case-control study. The research variables consisted of independent variable (obstetric risk factors include: parity, episiotomy, vacuum delivery, birth weight, prolonged second stage) and dependent variable (anal incontinence).

The research was conducted in Dr. Wahidin Sudirohusodo Teaching Hospital and its network, Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Hasanuddin, Makassar.

The sample was all women aged 20-55 years who had a history of vaginal delivery without any comorbid diseases, willing to participate and signed the informed consent. A self administered questionnaire filled out by the respondents and the anal incontinence were scored. The collected data were analyzed. Data analysis were conducted using SPSS with 2 x 2 table to get an odds ratio, where the significance is determined by the value of $p < 0.05$.

RESULTS

A total of 300 subjects were involved in this study. Majority of the respondents were aged less than 35 years, 171 (57%) and 129 (43%) were aged greater than or equal to 35 years. The majority of the samples were highly educated as much as 221 (73.7%) while less educated were 79 (26.3%). In terms of occupation, most of the samples did not work, 195 women (65%) and the counterpart were 105 (35%). The majority of respondent has normal body mass index as much as 207 (69%), over-weight 70 (23.3%), underweight 15 (5%) and obesity 8 (2.7%). In terms of obstetric history, the majority of the sample had children less than 3 as much as 185 (61.7%). The samples have experienced an episiotomy was 104 (34.7), the assisted delivery with vacuum experienced by 32 people (10.7%) and had delivered a baby more or equal to 4000 g as much as 12 (4%). Women with a history of prolonged second stage were 45 people.

Table 1. Respondents' Characteristics

Characteristics	Frequensi (n)	%
Age (years)		
< 35	171	57
≥ 35	129	43
Education		
Low (< 9 years)	79	26.3
High (≥ 9 years)	221	73.7
Occupation		
Not Working	195	65
Working	105	35
Body Mass Index		
Underweight	15	5
Normal weight	207	69
Over weight	70	23.3
Obesity	8	2.7

Parity		
< 3	185	61.7
≥ 3	115	38.3
History of Episiotomy		
No	196	65.3
Yes	104	34.7
History of Vacuum Extraction		
No	268	89.3
Yes	32	10.7
History of Large Baby		
No	288	96
Yes	12	4
History of prolonged second stage of labor		
No	255	85
Yes	45	15
Total	300	100

Bivariate analysis examines the relationship between parity and anal incontinence in women with a history of vaginal delivery. It shows that there is a significant relationship between parity and anal incontinence, p-value is 0.026 (p value <0.05 with OR (95% CI) = 1.806 (1.07- 3:03)). Women with parity more than or equal to three are more likely to having anal incontinence 1.8 times compared with their counterparts (Appendix, Table 1).

The result shows that there is no significant associaton between episiotomy as well as history of deliver large baby and anal incontinence in women with a history of vaginal delivery. However there is a significant association between a history of delivery with vacuum as well as prolong second stage of labor with the incidence of anal incontinence with p value 0.018 (OR (95% CI) = 3.65 (1.24 to 10.74)) and 0.006 (OR (95% CI) = 2.91 (1.24-6.78)), respectively. Women who have a history of vacuum and prolong of second stage of labor is 3.65 and 2.91 times more likely to suffer from anal incontinence compared with their counter parts, respectively. (Appendix, Table 2).

Table 2. The Association Obstetric Risk Factor and Anal Incontinence among Women with History of Vaginal Delivery

Obstetrics Risk factor	**Anal Incontinence**				**Total**		**p value**	**OR (95 CI)**
	Yes		**No**					
	n	**%**	**n**	**%**	**n**	**%**		
Parity								
>= 3	87	75.7	28	24.3	185	100	0.026*	1.806 (1.07-3.03)
< 3	117		68		115	100		
History of Episiotomy								
Yes	74	71.2	30	28.8	104	100	0.236	
No	130	66.3	66	33.7	273	100		
History of Vacuum Extraction								
Yes	28	87.5	4	12.5	32	100	0.018*	3.65 (1.24-10.74)
No	176	65.7	92	34.3	268	100		
History of baby > 4000 gr								
Yes	10	83.3	2	16.7	12	100	0.202	
No	194	67.4	94	32.6	288	100		
Prolonged second stage of labor								
Yes	38	84.4	7	15.6	45	100	0.006*	2.91 (1.24- 6.78)
No	166	65.1	89	34.9	255	100		
Total	204	68	96	32	300	100		

** Fischer Exact Test*

DISCUSSION

This study found that women who has anal incontinence is more than 50%. This percentage is quite higher related to definition of anal incontinence we used. It includes of flatal, liquid and stool incontinence.

The study found that parity had a significant relationship with the incidence of anal incontinence in women with a history of vaginal delivery. Contrary to our results, a study done by Fritel (2007), in 2640 women in France showed that parity does not have a significant relationship with the incidence of anal incontinence. However, most surveys found parity as risk factors for anal incontinence. It is said that the first vaginal delivery gives the greatest risk of new onset incontinence anal.[10]

In this study, there was no significant relationship between the incidences of episiotomy with anal incontinence. In line with this study, the research conducted by Fritel (2007), in France in 2640 women shows that there is no significant relationship between the incidences of episiotomy with anal incontinence.

In this study it was found that delivery by vacuum has a significant relationship with the incidence of anal incontinence. Delivery by vacuum was found to be a risk factor for sphincter laceration and anal incontinence. Manometric examination shows that anal squeeze pressure significantly decreased after spontaneous labor and asissted delivery.[7] Labor manometry provide as an objective evaluation function of the anal sphincter, which reflects the effect of a combination of structural and functional components (especially the internal and external anal sphincter). One of the consistent findings from multiple studies is that anal squeeze pressure was significantly decreased after spontaneous vaginal delivery and instrumental. The majority of studies indicate a problem with anal squeeze pressures as a result of vaginal delivery, regardless of continence status or sphincter integrity.[11]

In the case of anal resting tone, some prospective studies shows a significant decrease in postpartum resting pressures compared with antepartum in people suffering structural damage and underwent instrumental delivery.[7]

The internal anal sphincter is a circular smooth muscle that is responsible for 50-85% of the resting tone. Several studies indicated that the internal anal sphincter injury occurred up to 35% of women throughout labor but in this case also usually associated with damage to the external anal sphincter.[11]

Many cases occur where sphincter incontinence morphologically intact but compromised in terms of sensation. Pelvic wall are very susceptible to trauma caused by stretching, especially at the time of delivery. The rectum does not have proprioseptor and only owned by the levator, puborectalis and anal sphincter which supply the sensation of stretching and wrinkling of the rectal wall. These sensations are supplied along the pudendal nerve to the end of S2, S3 and S4.[7] If there is an injury to the pudendal nerve or its branch, the sensation of the continence will be disrupted. The response of the external anal sphincter to increased intra-abdominal pressure, dilated anal and rectal distension is in the form of contraction. In normal conditions, these contractions can last 40-60 seconds to allow time for the rectum to accommodate the feces, but in vaginal delivery or emergency caesarean section where there is trauma or excessive stretching of the birth canal can result in the abnormal contraction of external anal sphincter causing incontinence.[7]

This study found no significant relationship between large baby (≥ 4,000 grams) with the incidence of anal incontinence. Other studies have shown a relationship between anal incontinence and fetal weight over 4000 grams.[12]

The result of this study in line with the other that found a statistically significant association between prolonged second stage of labor and anal incontinence.[12] At the time of delivery, the descent process of the head on the pelvic wall can stretch the pelvic and the pudendal nerve. The nerve consists of sensoric and motoric nerve fibers that are very susceptible to stretching or trauma. Histological study showed that there is a necrosis in the muscular wall of the pelvis and the electromyographic study found reinnervation of pelvic wall on the pudendal nerves. This is due to injury of pelvic wall during labor.[7]

In our study, there are several limitations. Like most other case-control study that using a self-administered questionnaire, it has recall bias as obstetric history of respondents obtained solely from the patient recall and not based on medical records. In addition, complaints about

incontinence ranging from flatus, liquid to solid are assessed subjectively from the patients and confirmation test can not be done. Even so, several other studies have also used the same questionnaire as a baseline study to assess the risk factors. As a strength of ours, only limited study has been conducted in Indonesia. Previous research conducted in Bali incommunities over 60 years. This study examines the age of 20 to 55 years in order to specifically identify the obstetric risk factors in earlier symptomps.

CONCLUSIONS AND RECOMMENDATIONS

The researchers concluded that women has three or more children, having history of vacuum and prolonged second stage of labor were more likely to have anal incontinence than women in their counterpart. Researchers suggested that the socialization of obstetrics risk factor related to anal incontinence needs to be improved in community. Moreover, improving the skills of midwives and health care personnel in order to minimize the birth trauma and prolonged second stage of labor is needed as a process for preventing anal incontinence.

REFFERENCES

1. Fritel X, Ringa V, Varnoux N, Zins M, Breart. Mode of Delivery and Fecal Incontinence at Midlife: a Study of 2640 Women in the Gazel Cohort. Obstet Gynecol. 2007: 31-8.
2. Trowbridge. Updates on the treatment of the fecal incontinence. Virginia: ACG/VGS/ODSGNA Regional Postgraduate Course. Female Pelvic Medicine and Reconstructive Sur. 2014: 1-20.
3. Whitehead WE, Borroud l, Ye W. Fecal incontinence in U.S. adults: Epidemiology and Risk Factors. Gastroenterol. 2009; 137: 512-7.
4. Suyasa IG. Prevalence of Fecal Incontinence in Community Dwelling Older People in Indonesia. National Conference on Incontinence. Melbourne: Victoria. 2011: 1-15.
5. Rush. Fecal Incontinence. Rush University Medical Centre. 2013: 1-3.
6. Scott. Risk Factors in Fecal Incontinence. In Ratto C & Doglietto G. Fecal Incontinence Diagnosis and Treatment. Italy: Springer. 2007: 43-4.
7. Bharucha E, Blanon ER. Anatomy and Physiology Continence in Ratto C & Doglietto G; Fecal Incontinence Diagnosis and Treatment. Italy: Springer. 2007: 3-10.
8. Moore. Fecal incontinence: New Treatment Options. Sinai: Colorectal Cancer Centre Cedars-Sinai Med Center. 2012: 1-18.
9. Macmillan AK, Merrie AE, Marshal RJ, Parry BR. The Prevalence of Fecal Incontinence in Community-Dwelling Adults: A Systematic Review of the Literature. Dis Colon Rectum. 2007; 4: 1341-9.
10. Laine K, Skjeldelstad FE, Sanda B, Horne H, Spydslaug A. Prevalence and Risk Indicators for Anal Incontinence. Hindawi Publishing Corporation. ISRN Obstet Gynecol. 2013: 1-8.
11. Sultan. Perineal and Anal Sphincter Trauma Diagnosis and Clinical Management. London: Springer-Verlag. 2007: 3-45.
12. Hatem M, Pasquier JC, Fraser W, Lepire E. Factors Associated With Postpartum Urinary/Anal Incontinence in Primiparous Women in Quebec. J Obstet Gynaecol Can. 2007; 29(3): 232-9.

Research Article

Incidence of Pelvic and Paraaortic Lymph Node Metastasis in Epithelial Ovarian Cancer at a Tertiary Care Center

Insidensi Metastasis Kelenjar Getah Bening Pelvis dan Paraaorta pada Kanker Epitel Ovarium di Suatu Rumah Sakit Tersier

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Abstract

Objective: To investigate the incidence of pelvic and paraaortic lymph node metastasis in epithelial ovarian cancer.

Methods: This was a cross-sectional study. Data were collected from medical records, and from the cancer registry 1539 medical records were obtained. From there, 863 patients were operated and 676 were not, and only 401 medical records were found complete, and 306 samples were excluded because they have been treated with NAC and underwent surgery, patients who underwent surgery but the results is not the epithelium, and patients who underwent surgery, but the results were benign or borderline. And 95 patients who underwent primary surgery and lymphadenectomy only 55 patients have results in lymphadenectomy. This study uses a calculation of sample size with categorial descriptions, with precision of 3% then obtained a minimum sample size of 261 patients.

Results: According to the characteristics of the study subjects above, the results were stage I, II, III respectively 60%, 10.9%, and 29%. The metastasized of the lymph node paraaortic 9.1%, and pelvic/paraaortic 20% pelvic/paraaortic23.6%. Based on the degree of differentiation the results were good differentiation 30.9%, moderate differentiation 23.6%, and poor differentiation 45.5%. We found that paraaortic lymph node metastasis were most frequent at stadium III (43.8%). In relationship between lymph node metastasis with differentiation of epithelial ovarian cancer, the most frequent epithelial ovarian cancer were one with poor differentiation in pelvic/paraaortic lymph node with the sum of 69.2%. From analysis, there is significant difference between serous hystologic subtype with mucinosum subtype in pelvic lymph node, significant difference between serous hystologic subtype and clear cell in paraorta or pelvic lymph node and between the serous histology subtype and mucinous as well.

Conclusion: Lymph node metastasis incident of ovarian epithelial cancer in paraaorta amounts 20%, pelvic 9.1% and pelvic or paraaortic 23.6%. Higher the stadium, the lymph node involvements will be higher as well (pelvic and paraaortic). In stadium 1 of mucinous subtype with well differentiation has minimal lymph node involvement so we can be more selective in considering the risk and benefit of lymphadenectomy.

[Indones J Obstet Gynecol 2018; 6-1: 60-63]

Keywords: lymph node metastasis, ovarian cancer

Abstrak

***Tujuan**: Mengetahui insiden metastasis kanker ovarium epitelial yang dilakukan pembedahan primer pada kelenjar getah bening pelvik, paraaorta dan pelvik/paraaorta di Rumah Sakit Dr. Cipto Mangunkusumo periode Januari 2009 - Desember 2015.*

***Metode**: Penelitian ini menggunakan desain penelitian potong lintang, data diambil dari rekam medis, dari data kanker register didapatkan 1584 daftar rekam medik, namun didapatkan 425 pasien kanker ovarium, dan 331 yang ekslusi, didapatkan 55 data yang masuk kriteria inklusi.*

***Hasil**: Dari 55 sampel yang dilakukan pembedahan primer pada kanker ovarium tipe epitel. Penyebaran kelenjar getah bening pada kanker epitel ovarium yang dilakukan pembedahan primer pada KGB paraaorta adalah 20%, pelvik 9,1% dan pelvik/paraaorta 23,6%.*

***Kesimpulan**: Insiden metastasis KGB kanker epitel ovarium pada paraaorta sebanyak 20%, pelvik 9,1% dan pada pelvik/paraaorta 23,6%. Semakin tinggi stadium, maka semakin tinggi keterlibatan KGB (pelvik dan paraaorta). Pada subtipe serosum lebih banyak menyebabkan keterlibatan pada KGB (pelvik dan paraaorta). Semakin buruk derajat differensiasinya, maka semakin tinggi keterlibatan pada KGB (paraaorta). Pada stadium I subtipe musinosum derajat difensiasi baik dengan keterlibatan pada KGB yang minimal sehingga dapat lebih selektif dalam mempertimbangkan risk dan benefit dari limfedenektomi.*

[Maj Obstet Ginekol Indones 2018; 6-1: 60-63]

***Kata kunci**: kanker ovarium, metastasis kelenjar getah bening*

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INTRODUCTION

Ovarian cancer is one of the most common gynecological cancers, after cervical and breast cancers. Ovarian cancer metastasized directly through extention and exfoliation, lymphatic and hematogenous.[1,2] Stage, cell types, and tumor histological differentiation influence the metastasis of ovarian cancer.[3] Lymphogenic metastasis most commonly found in retroperitoneal pelvic and paraaortic lymph nodes. Lymphogenic spread affects ovarian cancer prognosis.[1,4]

Lymphadenectomy in ovarian cancer is still a controversy.[3,5] Currently, there is no profound prospective study or randomized controlled trial (RCT) regarding its pathological anatomy, leading to this controversy. 1998 FIGO suggested that pelvic and paraaortic lymphadenectomy are an integrated part that could not be separated during ovarian cancer surgical staging.[6] Studies regarding lymphadenectomy are not profound enough. To date, there are no study published about the incidence of epithelial ovarian cancer lymph node metastasis at Dr. Cipto Mangunkusumo Hospital.

METHODS

This was a cross-sectional study. Data were collected from medical records, and the cancer registry. Of these, 863 patients underwent primary surgery and 676 were not, and only 401 medical records were found complete, and 306 samples were excluded because they have been treated with NAC and underwent surgery, patients who underwent surgery but the results is not the epithelium, and patients who underwent surgery, but the results are benign or borderline. And 95 patients who underwent primary surgery and lymphadenectomy only 55 patients have results in lymphadenectomy. This study uses a calculation of sample size with categorial descriptions, with precision of 3% then obtained a minimum sample size of 261 patients.

RESULTS

1539 medical records were obtained. According to the characteristics of the study subjects above, the results are Stage I, II, III respectively 60%, 10.9%, and 29%. The metastasized of the lymph node paraaortic 9.1%, and pelvic/paraaortic 20% pelvic/paraaortic 23.6%. Based on the degree of differentiation the results were good differentiation 30.9%, moderate differentiation 23.6%, and poor differentiation 45.5%.

Table 1. Sample Characteristics patien of Epithelial Ovarian Cancer Underwent Primary Surgery

Category	n	Percentage
Age :		
<30	1	1.8
31-40	11	20
41-50	23	41.8
>51	20	36.4
Clinical stadium :		
I	33	60
II	6	10.9
III	16	29.1
Lymph node metastasis :		
Pelvic	5	9.1
Paraaortic	11	20
Pelvic/paraaortic	13	23.6
Negative	42	76.4
Grade :		
NA	6	10.9
Well	16	29
Moderate	11	20
Poor	22	27.2
Histologisubtype :		
Brenner	1	1.8
Clear cell	23	41.8
Endometioid	13	23.6
Mucinous	11	20
Serous	7	12.7

The association between lymph nodes metastasis and cancer stadium are shown in Table 2. We found that paraaortic lymph node metastasis were most frequent at stadium III (43.8%) and the least frequent at stadium II (0%). From the statistical analysis we found significant difference in proportion value in pelvic, paraaortic and pelvic/paraaortic lymph node with higher value in stadium III than stadium I ($p<0.05$).

Table 2. Distribution of Pelvic, Paraaortic, and Pelvic/Paraaortic Lymph Node Metastasis in Epithelial Ovarian Cancer

Clinical stadium	Stadium I n=33		Stadium II n=6		Stadium III n=16		I vs II	I vs III	II vs III
Lymph node	**n**	**%**	**n**	**%**	**n**	**%**	**p value**		
Pelvic									
Positive	1	3	0	0	4	25	0.806	0.012*	0.064
Negative	32	97.0	6	100	12	75			
Paraaorta									
Positive	3	9.1	2	33.3	6	37.5	0.165	0.020*	0.823
Negative	30	90.9	4	66.7	10	62.5			
Pelvic/Paraaorta									
Positive	4	12.1	2	33.3	7	43.8	0.250	0.015*	0.599
Negative	29	87.9	4	66.7	9	56.2			

In relationship between lymph node metastasis with differentiation of epithelial ovarian cancer, the most frequent epithelial ovarian cancer were one with poor differentiation in pelvic/paraaortic lymph node with the sum of 69.2% and the least frequent were one well differentiated in pelvic lymph node (0%). From analysis, this study found significant difference in proportion value in paraaortic lymph node between those with poor differentiation compared with moderate differentiation, with $p<0.05$.

The most common incidence between lymph node metastasis with histologic subtype were shown in Table 2. Paraortic lymph node with branner histologic type amounts[1] 100% because the total of the samples in brenner is only 1, and the second most common is serous hystologic in paraaortic lymph nodes which is 42.9% and the least is mucinosum subtype in pelvic lymph node, amounted to 0%. There was significant difference between serous hystologic subtype with mucinosum subtype in pelvic lymph node, significant difference between serous hystologic subtype and clear cell in paraorta or pelvic lymph node, and between the serous histology subtype and mucinous as well.

Table 3. Distribution of the Histological Subtypes of Pelvic, Paraaortic, and Pelvic/Paraaortic Metastasis in Epithelial Ovarian Cancer

Histology	Clear cell n=23		Endometriosis n=13		Brenner n=1		Serous n=7		Mucinous n=11		Total n=55	
Lymph node	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Pelvic												
Positive	2	8.7	1	7.7	0	0	2	28.6	0	0	5	9.1
Negative	21	91.3	12	92.3	1	100	5	71.4	11	100	50	90.9
Paraaortic												
Positive	4	15.4	2	15.4	1	100	3	42.9	1	9.1	11	20.0
Negative	19	84.6	11	84.6	0	0	4	57.1	10	90.9	44	80.0
Pelvic/Paraaortic												
Positive	4	17.4	2	15.4	1	100	3	42.9	1	9.1	13	23.6
Negative	19	82.6	11	84.6	0	0	4	57.1	10	90.9	42	76.4

**p value < 0.05 ANOVA test*

There were significant differences in the pelvic lymph nodes obstained value higher proportion on serous histological subtype compare with mucinous type ($p<0.05$) were show in Table 5, and there were significant differences in the pelvic/ paraaortic lymph node metastases between clear cell histology subtype compared to serous, as well as between serous and mucinous histology subtype. However there were no significant difference in paraaorta lymph node.

DISCUSSION

In this study, we could not reach the minimum sample. From data subject characteristics showed that the spread of ovarian cancer by age at most in the age group 41-50 years by 41.8% this is in accordance with what was found in the literature that increasing age is a major risk factor for developing ovarian cancer, 50% of ovarian cancers diagnosed at the age of 65 years[1,7] The spread of lymph nodes obtained 23.6%, and the most to the lymph node paraaorta is 20% for deployment on paraaorta through lymphatic channels to follow along infudibulopelvikum ovarian vein and ended up in lymph nodes as high paraaorta renal blood vessels, according to the study.[8,9] This is in line with a review conducted in the Netherlands M. Kleppe et al (2011) were obtained from 14 studies that incident spread of lymph node on ovarian epithelial cancer was 14.2% (range 6.1-29.6%) where only the lymph node 7.1% and only 2.9 paraaortic % in the pelvic lymph nodes.[3,10]

CONCLUSIONS

The incidence of lymph node metastasis of ovarian epithelial cancer in paraaorta amounts 20%, pelvic 9.1% and pelvic or paraaortic 23.6%. Higher the stadium, the lymph node involvements will be higher as well (pelvic and paraaortic). In serous subtype, there is more incidents of lymph node involvements (pelvic and paraaortic). If the differentiation type is worse, there will be higher rate of pelvic and paraaortic lymph node involvement. In stadium 1 of mucinous subtype with well differentiation has minimal lymph node involvement so we can be more selective in considering the risk and benefit of lymphadenectomy. Further prospective studies are required to investigate the metastatic factors to lymph node more accurately.

REFERENCES

1. Barbara L Hoffman JOS, Joseph I Schaffer, Lisa M Halvorson, Karen D Bradshaw, F Gary Cunningham. Williams Gynecology Second edition. United States: McGraw-Hill; 2012; 876-74.
2. Jonathan S Berek MD M. Berek & Novak's Gynecology. California: Lippincott Williams & Wilkins; 2007: 103-6.
3. M Kleppea TW, T Van Gorp, BFM Slangen, AJ Kruse, RFPM Kruitwagen. Lymph node metastasis in stages I and II ovarian cancer: A review. Gynecol Oncol. 2011; 123: 610-4. Epub 6 October 2011. Elsevier Inc.
4. JL Benedet SP. Staging classifications and clinical practice guidelines of gynaecologic cancers. Int J Gynecol Obstet. 2000; 70: 207-312.
5. Roberto Angioli FP, Innocenza Palaia. Update on lymphadenectomy in early and advanced ovarian cancer. Lippincott Williams & Wilkins. Curr Opin Obstet Gynecol 2008; 20: 34-9.
6. John A Rock HWJ. Te Linde's operative gynecology. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2008: 1307-33.
7. Chu C, Hoskins W, et al. Primary Surgery for Ovarian Carcinoma. Global library of women medicine. 2011; 10: 1-21.
8. Andreas du Bois AR, Philipp Harter at al. Potential Role of Lymphadenectomy in Advanced Ovarian Cancer. Am Soc Clin Oncol. 2010; 28: 1733-40.
9. Burghardt GF, Lahousen M. Patterns of Pelvic and Paraaortic Lymph Node Involvement in Ovarian Cancer Gynecol Oncol 1991; 2: 103-6.
10. John K Chan BWD. Association of Lymphadenectomy and Survival in Stage I Ovarian Cancer Patients. Lippincott Williams & Wilkins. Am Coll Obstet Gynecol. 2007; 109: 12-9.

Research Article

The Effect of Cyclophosphamide Chemotherapy on Ovarian Anti-Müllerian Hormone Levels in Breast Cancer Patients

Efek Kemoterapi Siklofosfamid terhadap Kadar Hormon Anti-Müllerian Ovarium pada Penderita Kanker Payudara

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Abstract

Objective: To evaluate cyclophosphamide effects on Anti-Müllerian hormone (AMH) levels in breast cancer patients treated with cyclophosphamide chemotherapy.

Methods: This cohort prospective study was conducted in Dr. Wahidin Sudirohusodo Hospital in the Department of Obstetrics and Gynecology in collaboration with Department of Surgery, Faculty of Medicice, Universitas Hasanuddin between September 2015 and June 2016. Serum levels of AMH from forty breast cancer patients received three series of cyclophosphamide chemotherapy determined by Enzyme Linked Immuno Sorbent Assay (ELISA).

Results: Serum AMH levels decreased significant in the first series (from 2.09±2.04 μg/ml to o.65±1.06 μg/ml; p<0.05) through the third series (from 1.53±1.34 μg/ml to 0.5±0.65 μg/ml; p<0.05) of cyclophosphamide chemotherapy.

Conclusion: AMH levels decreased significant after cyclophosphamide indicated that cyclosphosphamide decrease ovarian reserve.

[Indones J Obstet Gynecol 2018; 6-1: 64-67]

Keywords: anti-müllerian hormone, breast cancer, cyclophosphamide, ovarian reserve

Abstrak

***Tujuan**: Menilai efek kemoterapi siklofosfamid terhadap kadar hormon Anti-Müllerian pada pasien kanker payudara yang dikemoterapi dengan siklofosfamid.*

***Metode**: Penelitian kohort prospektif ini dilakukan di RS Dr. Wahidin Sudirohusodo pada Departemen Obstetri dan Ginekologi bekerjasama dengan Departemen Bedah, Fakultas Kedokteran, Universitas Hasanuddin antara September 2015 dan Juni 2016. Pengukuran kadar serum AMH dari 40 pasien kanker yang mendapatkan tiga seri kemoterapi siklofosfamid menggunakan metode Enzyme Linked Immuno Sorbent Assay (ELISA).*

***Hasil**: Kadar serum AMH menurun signifikan dari seri pertama (dari 2,09±2,04 μg/ml menjadi 0,65±1,06 μg/ml; p<0,05) sampai seri ketiga (dari 1,53±1,34 μg/ml menjadi 0,5±0,65 μg/ml; p<0,05) pada kemoterapi dengan siklofosfamid.*

***Kesimpulan**: Kadar AMH menurun signifikan setelah kemoterapi siklofosfamid menunjukkan siklofosfamid menurunkan cadangan ovarium.*

[Maj Obstet Ginekol Indones 2018; 6-1: 64-67]

***Kata kunci**: anti-müllerian hormon, cadangan ovarium, hormon, kanker payudara, siklofosfamid*

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INTRODUCTION

Breast cancer is the most frequency malignancy in women in developed countries. It is estimated that approximately 7% of women with breast cancer are diagnosed before the age of 40 years, and this disease accounts for more than 40% of all cancer in women in this age group.[1] Breast cancer is likely to have a negative impact on reproductive function from the toxic effect of chemotherapy on ovarian follicles.[2] Young women with more primordial oocytes showed a significant reduction of their ovarian reserve following chemotherapy.[3] Chemotherapy causes acute loss of growing follicles resulting in premature ovarian failure, shortened reproductive life span and hormone deficiency.[4,5]

Cyclophosphamide, also known as cytophosphane, is a nitrogen mustard alkylating agent from the oxazophorine group. Cyclophosphamide is used to treat various types of cancer and some autoimmune disorders by slowing-down or stopping cell growth.[6] Cyclophosphamide, alone or in combination with other chemotherapy agents, is used for the treatment of lymphomas, some forms of leukemia, and some types of solid tumours including breast cancer. Gonadal failure is a major complication of cyclophosphamide administration,

especially in females.[7] Cyclophosphamide affects primordial follicle density rapidly after injection of this agent. Human coocytes are damaged drastically followed by ganulosa cells.[8]

The granulosa cells of primary follicles produced Anti-Müllerian Hormone (AMH).[9,15] AMH is a glycoprotein hormone belonging to transforming growth factor b family. It's levels reflect the continuous non-cyclical growth of small follicles.[10] Women with abnormal level of this hormone impaired the ovarian reserved followed by fertility.[11] This study aimed to evaluate the levels of AMH in breast cancer patients treated with cyclosphosphamide chemotherapy.

METHODS

This cohort prospective study was conducted in Dr. Wahidin Sudirohusodo Hospital in the Department of Obstetrics and Gynecology in collaboration with Department of Surgery, Faculty of Medicine, Universitas Hasanuddin between September 2015 and June 2016. The study protocol was approved by the Health Research Ethics Committee of Faculty of Medicine, Universitas Hasanuddin. Eligible patients were women with breast cancer, aged 20 to 48 years, who were to receive three series of cyclophosphamide treatment but who had not received chemotherapy previously. Prior chemotherapy, radiation therapy, oophorectomy, and patients who did not complete the first series of chemotherapy cycles until the third series were ineligible. Serum levels of AMH in each series of chemotherapy were measured at Prodia Clinical Laboratory Jakarta using AMH Enzyme Linked Immuno Sorbent Assay (ELISA) kits. Statistical analysis was performed using SPSS. A two-sided p value <.05 was considered statistically significant.

RESULTS

The study included 40 women with breast cancer who completed the three series of cyclophosphamide chemotherapy. Table 1 summarizes the characteristics of the patients. Seventy percent of the patients were aged 36-47 years, 52.5% had senior high school education, majority of patients had married (87.5%) and multiparity (51.4%).

Table 1. Subject characteristics

Variables	n	%
Age (years)		
29 - 35	12	30.0
36 - 47	28	70.0
Education		
SMP	12	30.0
SMA	21	52.5
College	7	17.5
Marital status		
Married	35	87.5
Unmarried	5	12.5
Parity		
0	3	8.6
1 - 2	14	40.0
> 2	18	51.4

Decreased serum AMH levels were seen after each series of cyclophosphamide chemotherapy; first series from 2.09±2.04 μg/ml to 0.65±1.06 μg/ml, second series from 4.03±3.47 μg/ml to 1.30±1.40 and third series from 1.53±1.34 to 0.50±0.65 μg/ml. There was an overall significant decrease in serum AMH levels ($p<0.05$) for the three series of chemotherapy (Table 2).

DISCUSSION

In reproductive-aged women treated with chemotherapy and radiotherapy for malignancy, serum AMH levels could be used to predict the ovarian

Table 2. AMH Levels in the Series of Cyclosphosphamide Chemotherapy of Breast Cancer

Series of chemotherapy	AMH levels (mean±SD μg/ml)		p
	Prechemotherapy	Postchemotherapy	
First	2.09±2.04	0.65±1.06	0.000
Second	4.03±3.47	1.30±1.40	0.003
Third	1.53±1.34	0.50±0.65	0.010

reserve.[12] Chemotherapy has a negative effect on the ovarium that cause the loss of primordial follicles, thus the levels of serum AMH as a marker for early prediction of the ovarian reserve.[13]

We found that there was a significant decrease in serum AMH levels in breast cancer patient treated with cyclophosphamide in the present study. AMH and inhibin B levels immediately decreased after chemotherapy.[14] AMH hormone is produced predominantly in primary, preantral, and small antral follicles.[15] The growing follicles appeared to be the target of chemotherapy agents.[14] Anders et al. conducted a study in AMH, E2, FSH, inhibin B, and AFC for markers of ovarian reserve in patients who received adjuvant treatment. They observed significantly decreased or undetectable serum AMH levels after chemotherapy similar to other previous studies.[16]

This study also found that AMH levels decreased after the first series and along with the next series of chemotherapy. Our results similar to previous study on breast cancer treated with cyclophosphamide that serum AMH levels decreased from first series (2.7±1.0 ng/ml) to second series (0.4±0.4 ng/ml).[14] Another study also assayed AMH and other hormonal markers before, during and after chemotherapy administration and reported the decreased serum AMH levels after chemotherapy indicating direct chemotherapy induced damage to the granulose cells and hence growing follicles and ultimately the follicle pool resulting in decreased ovarian reserved.[17]

AMH levels differ among breast cancer patients that received chemotherapy due to dose administration. Study found that difference dose correlated with AMH levels 0.52 ng/ml, 1.99 ng/ml and 3.09 ng/ml in high dose, low dose and not exposed to chemotherapy, respectively. Increased dose of chemotherapy has greater reduction in AMH levels (Gracia et al., 2012).[18]

AMH levels variations before, during and after chemotherapy provide information about the degree of follicle loss for each patient according to different chemotherapy regimens. Different patterns of AMH levels during the ovarian recovery phase make it possible to discriminate between high and low gonadotoxic chemotherapy protocols. In addition, pretreatment AMH levels are shown to predict the long-term ovarian function after the end of treatment. These provide a better understanding on the ovarian toxicity mechanisms of chemotherapy and to predict the degree of the ovarian follicle loss. Therefore, it can be useful for fertility preservation strategies, fertility counseling and future family planning.[19]

CONCLUSION

AMH levels decreased significant after cyclophosphamide chemotherapy. This is indicated that cyclosphosphamide decreased ovarian reserve.

REFERENCES

1. Anders CK, Johnson R, Litton J, et al. Breast Cancer Before Age 40 Years. Semin Oncol. 2009; 36(3): 237-49.
2. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. Hum Reprod Update 2009; 15: 32-9.
3. Partridge AH, Ruddy KJ, Gelber S, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. Fertil Steril. 2010; 94: 638-44.
4. Meirow D, Biederman H, Anderson RA, Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010; 53: 727-39.
5. Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer. 2007; 110: 2222-9.
6. Chen L, Waxman DJ, Chen D, Kufe DW. Sensitization of human breast cancer cells to cyclophosphamide and ifosfamide by transfer of a liver cytochrome P450 gene1. Cancer Res. 1996; 56: 1331-40.
7. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev Clin Oncol. 2009; 6(11): 638-47.
8. Oktem O, Oktay K. A novel ovarian xenografting model to characterize the impact of chemotherapy agents on human primordial follicle reserve. Cancer Res. 20071; 67(21): 10159-62.
9. Massague' J. The transforming growth factor-beta family. Annu Rev Cell Biol. 1990; 6: 597-641.
10. Anderson RA. What does anti-Müllerian hormone tell you about ovarian function? Clin Endocrinol. 2012; 77(5): 652-5.
11. Iverson A, Younis A, William J, et al. Inverse Correspondence of AMH and FSH levels in Women Presenting for Infertility Treatment. J South Carolina Academy Sci. 2011; 9(2): 1-4.
12. Anderson CY, Rosendahl M, Byskov AG, et al. Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod 2008; 23: 2266-72.
13. Steiner AZ, Stanczyk FZ, Patel S, Edelman A. Anti mullerian hormone and obesity: insights in oral contraceptive users. Contracept. 2010; 81(3): 245-8.
14. Rosendahl M, Andersen CY, la Cour Freiesleben N, et al. Dynamics and mechanisms of chemotherapy-induced ovarian follicular depletion in women of fertile age. Fertil Steril 2010; 94(1): 156-66.

15. Durlinger AL, Visser JA, Themmen AP. Regulation of ovarian function: the role of anti-Mullerian hormone. Reprod. 2002; 124: 601-9.
16. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008; 26(3): 286-95.
17. Visser JA, de Jong FH, Laven JS, Themmen AP. Anti-Müllerian hormone: a new marker for ovarian function. Reprod. 2006; 131(1): 1-9.
18. Gracia CR, Sammel MD, Freeman E, et al. Impact of cancer therapies on ovarian reserve. Fertil Steril. 2012; 97(1): 134-40.
19. Paigne M, Decanter C. Serum AMH level as a marker of acute and long-term effects of chemotherapy on the ovarian follicular content: a systematic review. Reprod Biol Endocrinol. 2014; 12: 26.