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EDITORIAL

A Red Card for Plagiarism

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INTRODUCTION

According to Kamus Besar Bahasa Indonesia, plagiarism is an act of copying against copyrights.[1,2] This includes copying texts, paragraphs, sentences, word, research content, opinion or idea, and admitting it as his or her own.[3,4]

A study on 40 students suspected of plagiarism has called the act of plagiarism as a destruction of academic integrity and honesty that has long been honored.[1]

A simple study conducted in Surakarta involving 20 teachers and 50 students in 5 Junior High Schools and 5 Senior High Schools in 2011 found that internet plagiarism is on the rise. This was found to be due to laziness and lack of references. The majority of teachers questioned in connection to the study, considered plagiarism as being acceptable as long as the task is submitted on time. Students who plagiarize tend to give up more easily, lack creativity, has difficulty controlling their emotions and show decline in achievement.[5]

It seems that plagiarism is an issue that needs to be tackled together. In 2009, the University of Indonesia published a decree issued by its Rector number: 208/SK/R/UI/2009 on the definition, act, prevention, and consequences towards plagiarism in academic circles within UI.[6] The Department of Obstetrics and Gynecology has also applied the same guidelines, by giving red cards to several residents. Other efforts established to prevent plagiarism include training and education on plagiarism and citation techniques in academic writing.

Cause

Information technology, also known as the internet, began to flourish in Indonesia in the 1990s, and brought about a major change in information exchange. As a result, an increase in plagiarism was observed, as literature published on the Internet is extremely easy to access and copy. Another important reason is limitations in English language capability, especially in countries where English is not used as the main language. Furthermore, a misperception on plagiarism and misunderstanding of correct citation techniques exists.[7]

A study by Ashworth and Banniter revealed that the cause of plagiarism is not solely rooted in the laziness of the student, but can also be explained because of an apparent misunderstanding on what the teacher has delivered and the task given, so that the student does not consider plagiarism as a moral issue.[8]

A study reported that 10-30% of plagiarism cases occurs due to citation error, including the absence of journal articles and authors. Several studies have discovered plagiarism in as much as 1 in 20 resident entrance test essay applications.[9]

Impact

Plagiarism may sound simple, but it carries an enormous and long-term impact. Students proven to commit the act of plagiarism were found to show unethical attitudes during his or her work.[9] These students also had a higher tendency to give up more easily, have lack of creativity, show difficulty in controlling emotion, and decline in achievement was also observed in these students.[5]

Strategies to Avoid Plagiarism

After considering the cause and impact of plagiarism, we hope that readers have the motivation to improve

their writing and citation skills in an effort to avoid plagiarism. Here are some points to avoid plagiarism.[10]

When writing an essay, do not only report or copy literatures or findings, but also add your interpretation, analysis, and argumentation based on those references. Use your own phrasing vocabulary, instead of copying words from the original author.

University education is not merely to obtain grades, but also a process to enhance the students' writing and research skills. When a problem occurs, a student should meet his/her academic tutor, module coordinator, or head of study program, and utilize available resources such as textbooks and training modules. When using others' sentences, use quotation and provide footnotes regarding the reference. If not, use your own words. When quoting a reference, immediately add the reference number or citation. This will help prevent unintentional plagiarism and assists in building a reference list. Articles on general knowledge do not require citations. When in doubt, place it in the reference list.

Although not recommended, when copying a sentence, use quotation and provide the correct source or reference. Nevertheless, rewriting a sentence from another reference with one's own words is advised. If the quote was modified, explain the modification. Do not copy a whole paragraph; read and rewrite with your own words. If you require material in significant amounts, paraphrase the material. If you need to display pictures, graphs, or tables; not only should references be specified, but a clear and complete explanation should also be provided.

CONCLUSION

Medical education requires students to have the ability to appraise literatures and write scientific articles. The burden of writing and providing citation causes the students to be prone to plagiarism. In the era of vastly expanding varieties of technology, the temptation to achieve something by way of a shortcut is commonly encountered. But do we have to get caught or punished first before understanding about plagiarism?

One simple concept in preventing plagiarism is to read more, in an effort to attain better writing ability. The same concept has been commanded by the Prophet Muhammad SAW when receiving the first verse in the Koran: "Iqra" (read).

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Research Article

Difference of Vertical Transmission in HIV-Infected Women with Complete and Incomplete PMTCT

PerbedaanTransmisi Vertikal pada Ibu Hamil HIV Positif dengan Prevention Maternal to Child Transmission (PMTCT) Lengkap dan Tidak Lengkap

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Abstract

Objective: To analyze any differences on vertical transmission in groups with complete and incomplete program as well as the factors influencing completion.

Method: This was a retrospective cohort study performed by data collection from medical records and/or interviews from January 2010 to February 2012. The variables analyzed subject characteristics, applied PMTCT program and risk factors affecting transmission.

Result: Seventy-five pregnant women who were HIV-positive were initially recruited, but 21 subjects were excluded due to incomplete medical records. In the first group (n=27) who received complete PMTCT, no vertical transmission was identified, while in the second group (n=27) with incomplete PMTCT, seven children were found to be HIV-positive. Rupture of membrane for more than 4 hours was the only significant risk factor for vertical transmission (p=0.001, RR=64.5, 95% CI=6.14-677.6).

Conclusion: There was a significant difference in the occurrence of vertical transmission between complete and incomplete PMTCT program. Complete PMTCT program may provide protective effect against the occurrence of vertical transmission by 25.9%.

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Keywords: HIV, PMTCT, vertical transmission

Abstrak

***Tujuan**: Untuk mempelajari perbedaan transmisi vertikal pada anak dari ibu hamil dengan HIV positif pada PMTCT lengkap dan tidak lengkap, serta faktor-faktor yang mempengaruhinya.*

***Metode**: Studi ini merupakan penelitian kohort retrospektif dengan mengambil data dari rekam medis dan/atau menghubungi ibu dengan HIV dari Januari 2010 sampai Februari 2012. Dikumpulkan karakteristik dari para subjek, program PMTCT yang dijalani dan faktor-faktor risiko yang dapat mempengaruhi transmisi vertikal.*

***Hasil**: Terdapat 75 ibu hamil dengan HIV positif namun hanya 54 pasang ibu-anak (72%) yang memiliki data lengkap. Pada 27 ibu hamil yang mendapat PMTCT lengkap tidak ditemukan transmisi vertikal, sedangkan pada 27 ibu hamil lainnya dengan PMTCT tidak lengkap ditemukan 7 anak yang positif HIV. Dengan regresi logistik didapatkan hanya ketuban pecah ≥4 jam yang menjadi faktor risiko terjadinya transmisi vertikal (p=0,001; RR=64,5; 95% IK 6,14-677,6).*

***Kesimpulan**: Terdapat perbedaan kejadian transmisi vertikal yang bermakna antara perempuan yang menjalani PMTCT lengkap dan tidak lengkap. Dengan melakukan PMTCT lengkap dapat memberikan efek protektif terhadap terjadinya transmisi vertikal sebesar 25,9%.*

[Maj Obstet Ginekol Indones 2015; 2: 69-75]

***Kata kunci**: HIV, PMTCT, transmisi vertikal*

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INTRODUCTION

According to the latest data from the World Health Organization (WHO), approximately 35.3 million people are currently living with the Human Immunodeficiency Virus (HIV), 30 million of which are living in lower-middle income countries, with approximately 2.3 million new infections in 2012.[1] HIV transmission occurs through contact with infected blood, organ transplantation, needle sharing, unprotected sexual intercourse, and vertical transmission from mother to infant. The risk of HIV transmission to infants in mothers who do not carry out any intervention is estimated to be about 15-45%.[2]

The estimated risk of HIV transmission during pregnancy is 5-10%, 10-20% during labor, and 5-20% during breastfeeding.[2,3] However, this can be lowered to less than 2% through antiretroviral prophylaxis given to the mother during pregnancy and child birth and the infants in the first weeks of life, as well as obstetrical interventions including elective cesarean surgery and avoidance of breastfeed-

ing. These interventions are known as the Prevention of Maternal To Child Transmission (PMTCT) or the prevention of mother-to-child vertical transmission.[1,4] Transmission to the child can be evaluated after 18 months of age, when anti-HIV antibodies that were transferred from the mother become undetectable. However, the evaluation can also be performed before 18 months by detecting viral DNA or RNA, viral culture, and IgA antibodies against HIV.[4]

In Indonesia, the proportion of HIV cases in women increased from 34% in 2008 to 44% in 2011, leading to an increase in HIV and AIDS transmitted from mother to baby. The number of HIV cases in children aged 0-4 years increased from 1.8% in 2010 to 2.6% in the following year.[4] Directorate General of Disease Control of the Indonesian Ministry of Health has developed a prevention program called "Pencegahan Penularan HIV dari Ibu ke Anak" (PPIA). Saroyo et al[5] has conducted a descriptive study in Dr. Cipto Mangunkusumo Hospital (RSCM) from January 2006 to December 2009 with the results of 174 HIV-positive pregnant women, but the HIV status of the baby is known in only 52 of them, and all were declared negative. They also revealed the difficulty to collect complete and sufficient data, and thus becoming a major bottleneck in the tracing of PMTCT data in RSCM.

The lack of integration of existing record system in Pokdisus HIV/Acquired Immune Deficiency Syndrome (AIDS), Department of Obstetrics and Gynecology, and Department of Pediatrics, causes difficulty in synchronizing data related to mother-to-child transmission during pregnancy, childbirth, and post-partum. In Indonesia, there is still limited data for vertical transmission, and also the number of HIV-infected pregnant women is likely to increase. Therefore, this study was conducted in order to assess the PMTCT program to see the outcome of vertical transmission in children from HIV-infected pregnant women during the period of January 2010-February 2012 at RSCM, which is expected to be a reflection of the government's effort to decrease the number of people living with HIV in Indonesia.

METHODS

Our study design is a retrospective cohort comparing vertical transmission of HIV occurring in infants born to HIV-positive pregnant women who received complete and incomplete PMTCT. It was conducted by collecting medical records of pregnant women who presented to the ER/delivery room and obstetrics outpatient clinic from January 2010 to February 2012, as well as the medical records of infants born from HIV-positive mothers from January 2010 to February 2012 and presenting to the pediatrics clinic or emergency room in RSCM. All the datas have to meet the inclusion and exclusion criteria.

The inclusion criteria are medical records of HIV-positive pregnant women as confirmed with either HIV rapid tests, ELISA or western blot for HIV antibodies, or by the viral load; all subjects being treated at RSCM, either from ANC or in the ER/delivery room from January 2010 to February 2012 and/or infants who seek treatment in the pediatric outpatient clinic or emergency department of RSCM who were born from HIV-positive mothers between January 2010 and February 2012, and also data regarding maternal and infant has to be completely stated in the medical records.

Subjects will be excluded if there were any anomaly/congenital abnormalities in the infants, contra indication of antiretroviral prophylaxis, no result of HIV antibodies of infants older than 18 months of age, and also breastfeeding mothers who have had problems in the breast and/or sores in the infant's mouth.

Complete PMTCT in this study is achieved when the mother has taken the ARV for at least 4 weeks before pregnancy[6], had underwent cesarean section, the infant has taken prophylactic ARV for 4-6 weeks, and had not been breastfed. PMTCT is considered incomplete when the subject does not meet one or more of the criteria of PMTCT.

Several risk factors have been stated to influence the occurrence of vertical transmission, which can be encountered during pregnancy such as high maternal viral load, sexually transmitted infections, maternal malnutrition; those encountered during childbirth, for example high maternal viral load, amniotic rupture ≥4 hours, invasive procedure during delivery, chorioamnionitis and CD_4 count; as well as breastfeeding. Those risk factors will also be analyzed.

This study was analyzed using SPSS 20.0 (IBM(C)) software. The independent variable was analyzed with unpaired categoric comparative analysis using Fisher's exact test. Confounding factors were analyzed using logistic regression. The ROC-

AUC curve analysis was performed to rank the highest predictor for vertical transmission. All significant variables were then included for multivariate analysis using logistic regression, from which the odds ratio (OR) for each variables could be ranked. Validation of the formula was done by computing the ROC, AUC, and Hosmer-Lemeshow test.

RESULTS

There were 75 pregnant women with HIV from January 2010 to February 2012. Only 72% of all the mother-infant pairs fulfilled the inclusion and exclusion criteria, of whom 27 pairs had complete PMTCT and 27 pairs had incomplete PMTCT. Characteristics of the study participants classified by completion of PMTCT can be seen in Table 1.

Table1. Subject Characteristics

Variable	Incomplete PMTCT n=27 (%)	Complete PMTCT n=27 (%)
Maternal ARV		
No ARV (<4 weeks)	27 (50.0)	0
ARV prophylaxis	0	13 (24.1)
Combination ARV (HAART)	0	14 (25.9)
Mode of delivery		
Vaginal delivery	8 (14.8)	0
Emergency Caesarean section	12 (22.2)	11 (20.4)
Elective Caesarean section	7 (13.0)	16 (29.6)
Infant prophylactic ARV		
No ARV	0	0
ARV prophylaxis	27 (50.0)	27 (50.0)
Breastfeeding		
Yes	0	0
No	27 (50.0)	27 (50.0)
CD_4 count (mother)		
<200 cell/mm^3	5 (9.3)	2 (3.7)
200-350 cell/mm^3	10 (18.5)	11 (20.4)
>350 cell/mm^3	10 (18.5)	14 (2.0)
Not examined	2 (3.7)	0
Viral load (mother)		
> 1000 copies/ml	0	2 (3.7)
< 1000 copies/ml	0	0
Undetected	5 (9.3)	4 (7.4)
Not examined	22 (40.7)	21 (38.9)
Viral load (infant)		
>100.000 copies/ml	0	0
<100.000 copies/ml	0	1 (1.8)
Undetected	13 (24.1)	8 (14.8)
Not examined	14 (25.9)	18 (33.3)
ELISA (infant ≥ 18 months)		
Positive	7 (13.0)	0
Negative	20 (37.0)	27 (50.0)

Variable	Incomplete PMTCT n=27 (%)	Complete PMTCT n=27 (%)
Pregnancy		
Singleton	27 (50.0)	27 (50.0)
Multiple	0	0
Gestational age at delivery		
35-36 weeks	4 (7.4)	6 (11.1)
37 weeks	23 (42.6)	21 (38.9)
Birth weight		
< 2500 gram	3 (5.6)	4 (7.4)
≥ 2500 gram	24 (44.4)	23 (42.6)
Sexually Transmitted Infections		
Yes	3 (5.6)	0
No	24 (44.4)	27 (50.0)
Malnutrition (during pregnancy)		
Yes	5 (9.3)	2 (3.7)
No	22 (40.7)	25 (46.3)
Membrane rupture		
≥ 4 hours	9 (16.7)	1 (1.8)
< 4 hours	18 (33.3)	26 (48.2)
Chorioamnionitis		
Yes	0	0
No	27 (50.0)	27 (50.0)
Invasive procedure		
Yes	0	0
No	27 (50,0)	27 (50.0)

Table 2. The Relationship Between PMTCT and Vertical Transmission in Infants ≥ 18 Months.

	Vertical transmission (+)		Vertical transmission (-)		p	cRR	95% CI
	n	%	n	%			
Incomplete PMTCT	7	25.9	20	74.1	0.010	0.741	0.593-0.926
Complete PMTCT	0	0	27	100.0			
Total	7	13.0	47	87.0			

In this study, we performed unpaired categoric comparative analysis using Fisher's exact test, because Chi Square test requirement were not fulfilled. This study compares the vertical transmission of HIV in children of pregnant women with HIV who complete and do not complete PMTCT. The children HIV status was seen from ELISA examination at age ≥18 months. At the age of <18 months, the viral load may be examined using PCR, but not all the children had the examination because it was more expensive than ELISA. To measure the strength of the relationship and because this is a cohort study design, we also calculated the relative risk (RR).

Table 2 shows there is a significant difference in vertical transmission between pregnant women receiving complete and incomplete PMTCT ($p<0.05$). Therefore, if we do complete PMTCT, it will provide a protective effect from vertical transmission of HIV in infants. The risk of vertical transmission was reduced by approximately 25.9% in patients with complete PMTCT (RR = 0.741).

The confounding variables that will be analyzed include the viral load, sexually transmitted infections, malnutrition in mothers, membrane rupture ≥ 4 hours, invasive procedure during delivery, chorioamnionitis and maternal CD4 cell count. Confounding variable of maternal viral load could not be analyzed because only nine subjects were examined, while maternal CD4 cell count during pregnancy cannot be analyzed either because the CD4 count for two subjects were not available. CD4 count can be analyzed by comparative analysis of numeric variables, but because the data distribution is not normal, the CD4 count can only be analyzed using non-parametric test.

Invasive procedures and choriamnionitis also can not be analyzed as there were no invasive procedures or chorioamnionitis in our samples. In multivariate analysis, only two variables were included, which were maternal malnutrition and amniotic membrane rupture. Sexual transmitted infection was excluded from the multivariate analysis because it does not meet the requirements with $p>0.25$.

With the backward LR method in logistic regression, it was found that only rupture ≥ 4 hours that have significant effect on vertical transmission in infants ≥ 18 months. Rupture of membranes ≥ 4 hours increased the risk 64 times compared to rupture of <4 hours. However, this risk needs to be analyzed further because the confidence interval was very wide.

DISCUSSION

We identified 75 pregnant women with HIV from January 2010 to February 2012, but were only able to include 54 women in our study due to incomplete data. We found that data in some medical records were not complete, suggesting pitfalls occurring at the time of registration and/or data entry. Some subjects had the wrong address, had moved, used a false identity to obtain insurance, or the possibility of a negative stigma because of the HIV causing the patient move out after delivery. This will affect the monitoring of ARV treatment and the effort to control HIV transmission, either horizontally or vertically. Women's program of the Asia Pacific network of people living with HIV, in a study with six Asian countries including Indonesia, has stated that the factors affecting access to health care for pregnant women with HIV-positive include a lack of knowledge and awareness, long distance to health facilities, the availability and costs (for transportation, services, laboratory tests, procedures, doctor and medication costs), the confidentiality of patient status and negative attitude coming from health service providers.[7] Three cases in this study revealed that the problem of stigma and discrimination from health care providers causes reluctance to come back for treatment.

The majority of subjects (53.7%) had graduated from senior high school, 22.2% graduated from junior high school, 16.7% have graduated university, and only 7.4% were elementary school graduates. In accordance with a 2001 report from UNAIDS stating that education plays an important role in predicting lifestyle adjustments; with higher level of education, exists a tendency to delay first sexual intercourse, and they will also be able to understand and react positively to the PMTCT program when they are pregnant. Three of the four subjects in this study only completed elementary school,with the tendency to be less concerned due to lack of understanding of HIV, which may also be influenced by the environment they live in, leading to a reluctance in following PMTCT.[8]

More than half of the subjects (59.2%) did not work, 31.5% had a stable job, and 9.3% did not have a permanent job. A woman who does not work has bigger dependence on their partner, causing their position in the family to become very small, and making them more vulnerable to get HIV. This is consistent with the trend of increasing number of housewives contracting HIV from her husband. As much as 79.7% of women in this study were infected through sexual intercourse, mostly obtained from their husbands who obtained HIV through intravenous drug use or unprotected sexual intercourse.[9]

Not all subjects obtained HIV from their husbands, there were 17 subjects whose husband's HIV status was negative, and were infected from their previous husband or from needle use. Data from 27 cohort studies with a total of 13,061 se-

rodiscordant couples in Sub-Saharan Africa as well as data from the Demographic and Health Survey with 1,145 serodiscordant couples in 14 countries concluded that 47% of heterosexual women with positive HIV status in a serodiscordant couple can remain in a good and stable relationship.[10]

In the complete PMTCT group, we did not find any children who were HIV-positive, while there were 7 children (13%) with positive HIV status in the incomplete PMTCT group. From the Fisher's test, we concluded that significant differences in vertical transmission can be encountered in complete and incomplete PMTCT with an RR of 0.741.

From Table 3, we can see that two steps of PMTCT were not performed in the seven subjects above, including not taking anti retroviral drugs during pregnancy and having vaginal delivery. However, one subject in our study also did not perform the two steps but no vertical transmission was encountered. This is possibly due to a very low or undetectable amount of HIV virus in the subject, limiting chance of transmission. Unfortunately, no data exists on the exact amount of virus that can explain the differences in outcome. Briand et al have studied the influence of method of delivery on the occurrence of vertical transmission, with the conclusion that vaginal delivery does not increase the risk of vertical transmission of HIV when the amount of virus in the prenatal period is controlled, with values varying between 50-1,000 copies/ml.[11]

Developed countries such as Canada have established a program to study the epidemic of vertical transmission in pregnant women by the name of the Canadian Perinatal HIV Surveillance Program (CPHSP), which was established in 1990 under the direction of the Canadian Pediatric AIDS Research Group. They performed data collection from the year 1990-2010 in all regions of Canada. The rate of transmission was only 0.4% when maternal HAART was initiated at least 4 weeks prior to delivery. Townsend et al also found the rate of vertical transmission in England and Ireland to be 0.8% when HAART is given at least 2 weeks before birth,[6] whereas in this study the administration of antiretroviral drugs during pregnancy is only 26%, with no vertical transmission (0%).

From the logistic regression analysis of the confounding factors, the only condition with significant influence on vertical transmission is membrane rupture longer than 4 hours. Unfortunately, the data distribution of membrane rupture ≥ 4 hours is not normal, therefore we cannot observe the cut off point of time influencing the transmission, and only non-parametric test was performed. In Miami, a prospective cohort study with 717 subjects on rupture of membranes in pregnant women with HIV concluded that the perinatal transmission rate was 1% in women with membrane rupture for less than 4 hours and 1.9% when rupture occurred for 4 or more hours. For 493 women with a viral load of less than 1,000 copies/ml receiving combination ART in pregnancy, there were no cases of perinatal transmission identified for up to 25 hours of membrane rupture. Logistic regression demonstrated only viral load above 10,000 copies/ml as an independent risk factor for perinatal transmission ($p<0.001$, OR=164.4, 95% CI 10.96-2,465.7).[12]

In this study, the viral load data of the subjects were not complete so we cannot perform the analysis. The subjects in this study cannot routinely get their viral load tested due to economic factor.

Table 3. Characteristics of HIV-Positive Children

No	Gestational age	Membrane rupture (hour)	Birth weight (gram)	Mother ARV consumption	Mode of delivery	Infant prophylaxis ARV	Breast-feeding
1	>37 weeks	0	3600	No	Vaginal	Yes	No
2	>37 weeks	5	2900	No	Vaginal	Yes	No
3	>37 weeks	10	2800	No	Vaginal	Yes	No
4	>37 weeks	11	3100	No	Vaginal	Yes	No
5	>37 weeks	6	2400	No	Vaginal	Yes	No
6	>37 weeks	6	3300	No	Vaginal	Yes	No
7	>37 weeks	8	2600	No	Vaginal	Yes	No

Therefore, a prospective cohort should be conducted to make it easier to follow the subjects and do laboratory examination as desired by the researcher. However, this will require more funds than just taking data from the medical records.

This study found the incidence of HIV-negative children from HIV-positive mothers who completed PMTCT, with RR/OR<1, to indicate that complete PMTCT can be a protective factor towards the occurrence of vertical transmission in children. But the drawback of this study is the lack of samples, as our sample do not meet the minimum number. Thus, our study results can not be generalized and required further research with a larger sample. The limited number of sample is due to the limited time and the fact that data collection of HIV patients' medical records is still inefficient, so some people with HIV cannot be followed. Even though there are limitations, but this study affirms the prospect that doing PMTCT correctly can provide better outcome in terms of preventing vertical transmission.

At the International AIDS Society conference in July 2013, following a review of the available evidence, WHO issued a new set of ART guidelines recommending earlier initiation of ART at CD4 cell count of 500 cells/ml or less for all adults and children above 5 years. According to the 2013 treatment guidelines, WHO is targetting 15 million people with HIV to receive antiretroviral treatment and only 40,000 new cases of HIV in children in 2015 compared to 290,000 cases in 2012.[13,14]

The coverage of ARV recipients in Indonesia in 2009 was 3.8%, similar to the coverage in Nepal (3.3%), and far behind Cambodia (32.2%), India (17.4%) and Vietnam (32.3%).[7] It indicates that there is still much work to be done by the Ministry of Health to achieve the target set by WHO.

The results of this study may be used as an input for the Directorate General of Disease Control Ministry of Health in order to improve the coverage of PMTCT programs, improve data collection by developing a program as was done by the CPHSP in Canada, evaluate and improve the PMTCT program in Indonesia, help reduce the number of maternal and infant mortality due to HIV/AIDS and prepare the next generation with good and qualified children free from HIV.

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Research Article

Placental Growth Factor Levels in Preeclampsia Compared to Normal Pregnancy

Kadar Placental Growth Factor pada Preeklampsia dan Kehamilan Normal

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Abstract

Objective: To identify and analyze the differences in the levels of PlGF in preeclampsia and normal pregnancy.

Method: This was a cross-sectional observational qualitative study of PlGF in preeclampsia and normal pregnancy. The number of samples in case and control group was 30 in each groups.

Result: We found that mean of maternal age in the preeclampsia group was 28.53 years and 25.23 years in the control group. Mean parity in preeclampsia and control group was 2.33 and 1.56, respectively. Mean hemoglobin level in preeclampsia and control group was 11.97 and 11.99, respectively. Mean maternal blood glucose level was 87.0 in the preeclampsia group, and 87.9 in the control group. In the preeclampsia group mean urea concentration was 16.45, while it was 22.78 in the control group. Mean creatinine level was 0.92 in the preeclampsia group and 0.64 in the control group. Mean SGPT and SGOT in the preeclampsia group was 23.36 and 21.97, while in the control group was 29.86 and 26.20. Test results showed that PlGF levels was significantly different between the preeclampsia and control group. Mean PlGF in the preeclampsia and control group was 42.10 and 452.33 respectively, with p <0.001.

Conclusion: We can conclude that the level of PlGF in the preeclampsia group is lower than the normal pregnancy group.

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Keywords: angiogenic factors, PlGF, preeclampsia

Abstrak

***Tujuan**: Mengetahui dan menganalisis perbedaan kadar PlGF pada preeklampsia dan kehamilan normal.*

***Metode**: Penelitian ini adalah penelitian kuantitatif observasional menggunakan pendekatan potong lintang kadar PlGF pada preeklampsia dan kehamilan normal. Jumlah sampel pada masing-masing kelompok kasus dan kontrol adalah 30 orang.*

***Hasil**: Dari hasil penelitian kami, didapatkan bahwa rerata variabel umur ibu hamil pada kelompok preeklampsia adalah 28,53 tahun, sedangkan pada kelompok kontrol adalah 25,23 tahun. Rerata paritas untuk kelompok preeklampsia dan kontrol adalah 2,33 dan 1,56. Rerata kadar hemoglobin adalah 11,97 untuk kelompok preeklampsia dan 11,99 untuk kelompok kontrol. Untuk rerata GDS ibu pada kelompok preeklampsia 87,0, kelompok kontrol adalah 87,9. Pada kelompok preeklampsia didapatkan rerata ureum sebesar 16,45 dan 22,78 untuk kontrol. Rerata kreatinin 0,92 untuk preeklampsia dan 0,64 untuk kelompok kontrol. Pada rerata SGPT dan SGOT pada kelompok preeklampsia 23,36 dan 21,97, sedangkan pada kelompok kontrol sebesar 29,86 dan 26,20. Hasil pemeriksaan kadar PIGF menunjukkan bahwa terdapat perbedaan signifikan antara kelompok preeklampsia dan kelompok kontrol. Pada kelompok preeklampsia didapatkan rerata PlGF sebesar 42,10 dan 452.33 untuk kontrol dengan p<0,001.*

***Kesimpulan**: Berdasarkan analisis hasil penelitian didapatkan kesimpulan bahwa kadar PlGF pada kelompok preeklampsia lebih rendah daripada kelompok dengan kehamilan normal.*

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***Kata kunci**: faktor angiogenik, PlGF, preeklampsia*

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INTRODUCTION

Preeclampsia is a contributor to maternal as well as perinatal morbidity and mortality, with rate of preeclampsia in all pregnancy estimated to be 5%.[1,2] Although the etiology of preeclampsia is definitely unclear, it is suspected that the presence of endothelial dysfunction plays an important role in the development of preeclampsia.[2-4] Preeclampsia is a clinical diagnosis, with the classic definition of preeclampsia consisting of three components; hypertension (blood pressure >140/90 mmHg in women who previously had normal blood pressure); proteinuria (>300mg/24 hours or +2 on urinalysis examination in the absence of urinary tract infection); and edema. However, a recent consensus excluded edema as a criterion for diagnosing preeclampsia. So far, screening tests and prevention of preeclampsia have not been available. Complications resulting from preeclampsia include eclampsia, hemolysis, elevated liver enzymes, low platelets (HELLP syndrome), disseminated intra-

vascular coagulophaty (DIC), hypertensive emergency, hypertensive encephalopathy and blindness in cortical regions.[4,5]

In the United States, preeclampsia 23.6 cases occurs in every 1000 delivery.[6,7] The incidence of preeclampsia in Indonesia was 3-10% and accounted for 39.5% of maternal mortality in 2001 and increased to 55.56% in 2002.[8]

Although preeclampsia has been studied extensively for numerous decades, the etiology and pathogenesis of this disease remains unclear. Currently many theories trying to explain the etiology and pathogenesis of preeclampsia exist, including genetic predisposition, thrombophilia, endocrinopathy, vasculopathy, placental ischemia, oxidative stress, and immune maladaptation.[9,10]

Preeclampsia is mostly believed to occur in two stages. The first stage is the preclinical stage, which is a process of endothelial disruption and inadequate cytotrophoblast invasion of the spiral arteries in the myometrium. This poor placentation process leads to ischemia and hypoxia in the placenta. The second stage occurs in late pregnancy, where the presence of placental oxidative stress causes the release of anti-angiogenic proteins such as soluble Fms-like Tyrosine Kinase-1 (sFlt-1), prostaglandins and cytokines into the maternal circulation. On the other hand, the state of oxidative stress will suppress the production of pro-angiogenic factors, including placental growth factor (PlGF) and vascular endothelial growth factor (VEGF).[11]

There was growing evidence about the imbalance between angiogenic factors, such as PlGF and VEGF, with angiogenesis inhibiting factors, such as sFlt-1 and soluble Endoglin (zinc), in the pathogenesis of preeclampsia. sFlt-1 was found to be responsible for the syndrome of preeclampsia. In a study of animals given exogenous sFlt-1, symptoms of preeclampsia such as hypertension, proteinuria and kidney damage was shown. sFlt-1 is increased in preeclampsia, and decreased to normal levels after birth. In contrast with sFlt-1, PlGF concentrations decreases in preeclampsia.[12] Levine et al reported that the increase of sFlt-1 as a result of endothelial dysfunction caused a decrease of free PlGF in serum preeclampsia.[13] Soluble Fms-like Tyrosine Kinase-1 is an antagonist of PlGF and VEGF, are bound and prevents the interaction of PlGF and VEGF in endothelial surface receptors.[14,15]

The balance between PlGF, VEGF (pro-angiogenic factors) and sFlt-1 (anti-angiogenic factors) is important in the process of angiogenesis, vasculogenesis and placental development during pregnancy.[16]

PlGF is a member of the VEGF polypeptide family. In recent times, it has been observed that serum PlGF level at mid-pregnancy is significantly lower in obese women. It has been established that PlGF could be an effective predictor of preeclampsia in the early second trimester of pregnancy. However, some researchers also considered PlGF to be more effective as a biomarker in high-risk populations although the predictive value of these biomarkers appear to be limited in early onset preeclampsia.[17,18] Based on this, the researchers intend to conduct a study to determine and analyze the differences in the levels of PlGF in preeclampsia and normal pregnancy.

METHODS

We carried out a cross-sectional observational qualitative study of PlGF in preeclampsia and normal pregnancy. This study was conducted in the Department of Obstetrics and Gynecology, RSUP Prof. Dr. RD Kandou from September to October 2013.

Patients with preeclampsia and normal pregnancy presenting in the outpatient unit who meet the inclusion criteria and provided informed consent after receiving explanation about the procedure of this study. Inclusion criteria include women with preeclampsia or normal pregnancy, at term, gave birth in RSUP Prof. Dr. RD Kandou, Manado, and willing to participate in this study. Women having chronic diseases such as diabetes mellitus, cardiovascular or kidney abnormality, chronic hypertension, multiple pregnancy, IUFD, premature rupture of fetal membranes, intrauterine infection, congenital malformation, or placental abnormalities (hemangiomatous placenta or placenta previa) were excluded from this study. The sample size needed to meet 90% power of this study was 30 subjects in each preeclampsia and control group.

About 10 ml of blood sample was taken from the cubital vein, 5 ml for PlGF serum assay and 5 ml for blood sugar, SGOT, SGPT, ureum, creatinine, hemoglobin, leukocyte and total protein test. The blood tests, except for PlGF assay, were done in RSUP Prof. Dr. RD Kandou laboratory. Blood for PlGF assay was centrifuged at 2000-3000 rpm for

15 minutes and then stored in the freezer with a temperature of -20°C before it was sent to Prodia Laboratory in Jakarta in an ice pack to maintain the temperature. PlGF was tested quanitatively using ELISA.

Serum PlGF data from the preeclampsia and control group was collected and compared statistically using t-test. Data analysis was done using SPSS 17.0 for Windows.

RESULTS

The subjects of this study were 60 pregnant women at term that met the inclusion criteria. They were allocated into 2 groups, preeclampsia as the case group and normal pregnancy as the control group. Baseline characteristics of our subjects are shown in Table 1.

From this study, we found that the mean maternal age in the preeclampsia group was 28.53 years, and 25.23 years in the control group. The mean parity in preeclampsia and control group was 2.33 and 1.56, respectively. Mean hemoglobin and maternal blood glucose was similar in both groups. Moreover, in the preeclampsia group mean urea level was 16.45, while it was 22.78 in the control group. Mean creatinine was 0.92 in the preeclampsia group and 0.64 in the control group. Mean SGPT and SGOT in the case group was 23.36 and 21.97, while it was 29.86 and 26.20 in the control group.

Table 1. Baseline Characteristics

Characteristics	Control Group		Preeclampsia	
	Total (n)	Percentage (%)	Total (n)	Percentage (%)
Age				
<20 years	14	56.67	14	56.67
20-24 years	3	10.0	3	10.0
25-29 years	5	16.67	5	16.67
30-35 years	8	26.67	8	26.67
Weight				
<60 kg	7	23.3	7	23.3
60-79 kg	20	66.6	20	66.6
80-100 kg	3	10.0	3	10.0
>100 kg	-	-	-	-
Education level				
High school	2	6.67	2	6.67
Junior high school	5	16.67	5	16.67
Senior high school	19	63.33	19	63.33
College	4	13.33	4	13.33
Occupation				
Housewive	14	56.67	14	56.67
Civil servant	6	20.0	6	20.0
Private company	10	33.33	10	33.33
Ethnic group				
Minahasa	20	66.6	20	66.6
Sangihe	4	13.33	4	13.33
Gorontalo	4	13.33	4	13.33
Javanese	2	6.67	2	6.67

Table 2. Distribution of Study Variables

Variables	Group	N	Mean
Age (yo)	Preeclampsia	30	28.5
	Control	30	25.2
Parity	Preeclampsia	30	2
	Control	30	2
Hb (gr/dl)	Preeclampsia	30	11.9
	Control	30	11.9
Blood glucose (mg/ dl)	Preeclampsia	30	89
	Control	30	87
Ureum (mg/ dl)	Preeclampsia	30	16.4
	Control	30	22.7
Creatinin (mg/dl)	Preeclampsia	30	0.9
	Control	30	0.6
SGOT (U/l)	Preeclampsia	30	23.3
	Control	30	21.9
SGPT (U/l)	Preeclampsia	30	29.8
	Control	30	26.2

Serum PIGF level from preeclampsia and control group was collected and compared statistically using SPSS 17.0 for Windows. Mean PlGF in preeclampsia and control group was 42.10 and 452.33, respectively. Statistical analysis showed that PlGF levels in the preeclampsia and control group was significantly different. Using Mann-Whitney test we found that the difference of PIGF level between the control and preeclampsia group was statistically significant ($p<0.01$).

DISCUSSION

Preeclampsia is a complication of pregnancy presenting in the form of a syndrome with serious consequences for the mother and fetus. Incidence of preeclampsia was found to be 7% to 10%. This syndrome is characterized by the presence hypertension, proteinuria and multi-organ failure. Preeclampsia is considered as a multi-system syndrome, characterized by vasoconstriction, metabolic changes, endothelial dysfunction, activation of the coagulation cascade, and increased inflammatory response.[1]

Although preeclampsia has been studied extensively for several decades, the etiology and pathogenesis of this disease is still unclear. Angiogenesis is one of the important processes that play a role in the development of the vascular system of the placenta. Among several angiogenic factors, VEGF and PlGF play an important role in the vascular system of the placenta. It has been proven that an imbalance between angiogenesis factors such as VEGF and PlGF and antagonist of angiogenesis factors, such as sFlt-1, plays a major role in the pathogenesis of preeclampsia. Angiogenic factors PlGF and VEGF have an essential function for placental development and the effectiveness of endothelial cells.[9,10]

In normal pregnancy, serum PlGF concentration increases at 8-12 weeks gestation, peaks at 29-32 weeks gestation, and then declines at 33-40 weeks gestation.[11] In several studies, PlGF showed low levels in preeclampsia. PlGF levels in women who develop preeclampsia was found to be significantly lower than in normotensive pregnancies at 13-16 weeks gestation until the beginning of labor. In addition it was also reported that at the beginning of the second trimester (10 or 11 weeks), levels of PlGF in pregnancies that would evolve into preeclampsia was lower compared to normal pregnancy.[11,16]

PlGF has been proposed as a marker and mediator of endothelial dysfunction in preeclampsia. Some studies found that the concentration of PlGF in preeclampsia is 3 to 10 times lower than in normal pregnancy. PlGF concentration in preeclampsia begins to fall at 9-11 weeks before the onset of hypertension and proteinuria; or at least 5 weeks before the onset of this condition.[16]

Many studies have evaluated the levels of PlGF in preeclampsia compared with normotensive pregnancies. Krauss et al reported that out of all pregnancies with preeclampsia, 27.3% had PlGF levels below 200 pg/ml.[19] Bersinger et al found levels of PlGF in preeclampsia to be significantly lower than in normotensive pregnancy at term.[20] Likewise, Shen et al found levels of PlGF in pregnancies with preeclampsia to be significantly lower compared to normotensive pregnancies at the same gestational age.

This study is an observational study using quantitative cross-sectional approach to prove the existence of differences in the angiogenic factor (PlGF) in normal pregnancies and pregnancies with preeclampsia.

We found that the difference between mean levels of PlGF between the preeclampsia group and

normotensive group was significant ($p<0.05$), where levels of PlGF in the preeclampsia group was 42.10 pg/dl, and in the normotensive group was 452.33 pg/dl.

There are several explanations regarding the decreased levels of PlGF in pregnancies with preeclampsia. First, low levels of PlGF occur due to inadequate trophoblast proliferation into the maternal spiral arteries in early pregnancy. It may occur due to impaired renal function, capillary thickening, decreased perfusion and other mechanism. Looking at the results of this study and some previous studies, we can conclude that PlGF is very potential to be developed as a predictor of preeclampsia. By evaluating the PlGF levels in pregnant women as early as possible, we can predict the occurrence of preeclampsia and possibly prevent it.

Although the results of this study showed a significant difference between preeclampsia with normotensive pregnancies, this research has some limitations including the limited number of samples, so we could not determine the cut-off point of the occurrence of preeclampsia. Moreover, the study was limited to proangiogenic factor levels (PlGF) in term pregnancy. Research on early gestation until term is needed to allow us to clearly see the difference in the levels of angiogenic factors in normal pregnancies and pregnancies with preeclampsia. Furthermore, PlGF concentration is influenced by many factors, such as the presence of ischemic tissue, malignancy, inflammation and multiple other abnormalities. Therefore, changes in PlGF concentration are not only specific to preeclampsia.

CONCLUSION

Based on our study results, we can conclude that the level of PlGF in pregnancy complicated by preeclampsia is lower than in normal pregnancy. A multicenter study involving more participants who were observed from the beginning of pregnancy until delivery is needed in order to apply the results on the population of pregnant women in preventing preeclampsia.

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Research Article

User Profile and Factors Correlating to Duration of Intrauterine Device Use

Profil Pengguna dan Faktor yang Berkorelasi dengan Penggunaan Alat Kontrasepsi dalam Rahim

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Abstract

Objective: To determine the demographic and clinical profile of intrauterine device (IUD) users and factors correlating to duration of IUD use.

Method: We conducted a prospective observational study of 867 patients who underwent IUD insertion in Raden Saleh Outpatient Clinic during the period of January - December 2011. All patients were followed for 1 year to ascertain any complaint of discharge after insertion. Spearman correlation test was conducted to inves- tigate the strength of correlation and significance between age, parity, and discharge, with duration of IUD use.

Result: During year 2011, 867 patients (median of age=34 [range=14-49]; median parity=2 [range=0-7]) underwent IUD insertion in Raden Saleh Clinic. The majority of subjects were aged between 31-35 years old and were willing to use IUD for 4 years. Bivariate analysis revealed a significant correlation between age, parity, and vaginal discharge with duration of IUD use. The strongest correlation was identified between age and duration of use (r=0.25, p<0.001 for age and duration of use; r=0.19, p>0.002 for parity and duration of use; r=0.05 p=0.045 for discharge and duration of use).

Conclusion: Most IUD users were aged 31-35 years, who were willing to use IUD for 4 years. Factors that correlated with duration of IUD use were age, parity, and vaginal discharge.

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Keywords: contraceptive, duration of use, family planning, intrauterine device

Abstrak

***Tujuan**: Mengetahui profil karakteristik pengguna AKDR dan faktor yang berkorelasi dengan lama pemakaian AKDR.*

***Metode**: Kami melakukan penelitian prospektif observasional pada 867 pasien rawat jalan yang datang untuk melakukan pemasangan AKDR di Klinik Raden Saleh pada Januari-Desember 2011. Seluruh pasien diikuti selama 1 tahun untuk mengetahui munculnya keluhan keputihan. Uji korelasi Spearman dilakukan untuk mengetahui besar dan kemaknaan korelasi antara usia, status paritas, dan keluhan keputihan dengan lama pemakaian AKDR.*

***Hasil**: Selama tahun 2011 terdapat 867 pasien rawat jalan (median usia=34 tahun [rentang=14-49 tahun]; median paritas=2 [rentang=0-7]) melakukan pemasangan AKDR di Klinik Raden Saleh. Pengguna AKDR paling banyak berasal dari kelompok usia 31-35 tahun dan sebagian besar pasien merencanakan untuk memasang AKDR selama 4 tahun. Analisis bivariat menunjukkan adanya korelasi bermakna antara usia, paritas, dan keputihan dengan lama pemakaian AKDR. Kekuatan korelasi terbesar ditemukan pada korelasi antara usia dan lama pemakaian (r=0,25, p<0,001 untuk usia dan lama pemakaian; r=0,19, p>0,002 untuk paritas dan lama pemakaian, r=0,05, p=0,045 untuk keputihan dan lama pemakaian).*

***Kesimpulan**: Pengguna AKDR terbanyak ialah perempuan usia 31-35 tahun dengan rencana pemakaian selama 4 tahun. Faktor yang berkorelasi dengan lama pemakaian adalah usia, status paritas, dan keluhan keputihan.*

[Maj Obstet Ginekol Indones 2015; 2: 81-84]

***Kata kunci**: alat kontrasepsi dalam rahim, keluarga berencana, kontrasepsi, lama pengunaan*

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INTRODUCTION

Nowadays, reproductive health is still a global issue. The 5th Millennium Development Goal (MDG) aims to improve maternal health, but maternal mortality ratio as its parameter is still high.[1,2] Data from Survei Dasar Kesehatan Indonesia (SDKI) 2007 shows maternal mortality ratio in Indonesia to be 228/100,000.[1,3,4] Uncontrolled number of parity, very close pregnancy interval, and pregnancy in extreme age (too young or too old) are the main causes of maternal mortality and morbidity.[5,6] The definitive solution is clear, prevent the pregnancy. In this sense, family planning program and contraception plays a critical role.

Family planning program in Indonesia have been developed since 1984. The program is carried out by promoting contraceptive use. However, data from 2010 showed the prevalence of contraceptive use to be only 61.5%.[7,8] In 2008, the government and Ministry of Health began to promote postpar-

tum and post-miscarriage contraception, including hormonal contraception (pill, implant), IUD, barrier device (condom, diaphragm), and sterilization (vasectomy, tubectomy). Among those modalities, IUD was one of the least favorite options, with only 18.8% prevalence of use.[9,10] Moreover, the insertion procedure was thought to be too invasive, with most patients thinking IUD to be dangerous, thus hindering their decision to receive IUD. Women who are already users only use it for a very short period.[11] Women reported going back to a doctor several times just to check the presence of the device in the uterus. They also reported feeling uncomfortable due to a foreign object in their uterus. Others have complained of pain, vaginal bleeding, and copious discharge. The government is currently promoting education on those issues, but the content is still unorganized.[10] Therefore, this study was conducted to get the profile of IUD users and the factors correlating with duration of IUD use.

METHODS

We conducted a prospective-observational study of 867 patients undergoing IUD insertion in Raden Saleh Clinic. This study was carried out from January 2011 to March 2013. Sampling was conducted in the period of January 2011 to December 2011 using consecutive random sampling. Data was collected by interview conducted by one interviewer for all subjects.

The inclusion criteria include all IUD users without any restriction of age and IUD type. Exclusion criteria was subjects who refused to participate in this study. We collected patient characteristics including age, parity, and the plan for duration of IUD use. One-year follow up was carried out to ascertain the presence of vaginal discharge during IUD use.

Age will be categorized in groups of 5 years, while presence of vaginal discharge will be dichotomous. Data will be described to show the distribution of subjects' age, parity, duration of use, and vaginal discharge. Data will be presented in mean and standard deviation for normally distributed data or median and range for data that are not normally distributed. In addition, the data will also be presented in the form of charts to aid with visualization of data distribution.

Bivariate analysis was conducted with Spearman correlation test in order to show the correlation between age, parity, and vaginal discharge with duration of IUD use. Data were analysed using SPSS 17.0.

This study is in accordance with the principles of "Declaration of Helsinki" and principles in "Guideline for Good Clinical Practice" of ICH Tripartite Guideline, as well as local regulations in Indonesia. All subjects and her family received explanation about the whole procedure and the purpose of this study. They also signed the informed consent form.

RESULTS

In 2011, as many as 867 patients underwent IUD insertion in Raden Saleh Clinic. All patients were included in this study.

Median of age was 34 years old, with the youngest age found to be 14 years old and the oldest was 49 years old. The majority of patients used IUD after they had one (30%) or two children (33.7%). Only one patient used IUD before having any children. Duration of IUD use was in the range of 2-7 years, with most patients using IUD for 4 years (36.4%). Vaginal discharge was reported by 20 patients (2.3%). Demographics and clinical characteristics of our subjects are reported in Table 1.

Data showed that most IUD users belonged in the 31-35 years old age group. Vaginal discharge did not occur in all age groups. The complaint was identified mostly in the 21-25 years age group. The majority of patients used IUD for less than 5 years. Only 10% reported IUD use of more than 5 years.

Correlation test demonstrated the presence of a significant correlation between age, parity, and vaginal discharge with duration of IUD use (Table 2). The strongest correlation was identified between age and duration of use (r=0.25 for age, r=0.19 for parity, r=0.05 for vaginal discharge). The higher number of parity and age, the longer the duration of IUD use. Vaginal discharge was also shown to have a significant correlation with duration of use, but the correlation was very weak.

Table 1. Demographics and Clinical Characteristics of IUD Users in Raden Saleh Clinic January-December 2011 (n= 867)

Characteristics	n
Age (median, range)	34 (14-49)
Parity (n, %)	
0	1 (0.1)
1	260 (30.0)
2	292 (33.7)
3	212 (24.5)
4	65 (7.5)
5	22 (2.5)
6	4 (0.5)
7	1 (0.1)
Duration of IUD use (n, %)	
1 year	0 (0.0)
2 years	69 (8.0)
3 years	180 (20.8)
4 years	316 (36.4)
5 years	176 (20.3)
6 years	80 (9.2)
7 years	46 (5.3)
Vaginal discharge (n, %)	
Yes	20 (2.3)
No	847 (97.7)

Table 2. Correlation between Age, Parity, and Vaginal Discharge with Usage Duration

Correlation[1]	r	*p*
Age and usage duration	0.25	< 0.001
Parity and usage duration	0.19	< 0.001
Vaginal discharge and usage duration	0.05	0.045

[1] *Spearman correlation test*

DISCUSSION

This study discovered that the median of age of women undergoing IUD insertion in Raden Saleh Clinic in 2011 was 34 years old. Most patients belonged in the age group of 32-35 years old, constituting almost two times the number of that in the other age groups. The important finding is that the distribution of age of IUD users was not equal. IUD is more popular and more commonly used in older women, compared to women in their 20's.

Statistics show that uncontrolled number of parity, very close pregnancy interval, and extreme age (too young or too old) are the main causes of maternal mortality and morbidity.[7] The optimal age for pregnancy is 20-35 years old, with the interval between the first and second pregnancy being about 2-4 years. Therefore, contraception plays an important role, which is to prevent pregnancy before the age of 20 years, to manage and ensure the interval period between pregnancies, and to prevent pregnancy after 35 years. In regards to these roles, IUD as well as other contraceptive methods should be utilized equally in all age groups. The domination of IUD users in only one age group showed that the aim of contraceptives has not been achieved.

Previous studies with a similar purpose as this study was conducted by Singh et al in 1990.[12] The study was held in Benghazi, a developing country similar to Indonesia. The study found different results from ours, with IUD users mostly coming from the 20-29 years old age group and with a mean parity of 4. Similar to the findings in this study, they stated that IUD users were relatively older than users of other contraceptive methods. Furthermore, complication and discontinuation of IUD was reported to be higher than in other methods.

Vaginal discharge presents as the most common complaint among IUD users. Previous studies have demonstrated that the prevalence of bacterial vaginosis (BV) in IUD users was 9.3-37%.[13-16] Compared to the general population, Foda et al[17] found the prevalence of BV to be significantly higher among IUD users (12.64% vs 6.9%). Compared to other contraceptive methods, BV was also found to be higher among IUD users (37.0% vs 19.3%; p=0.03).[14] Vaginal discharge was the most common symptom of BV occurring in 41% of patients. This symptom brought patients back to the doctor to have the IUD checked, while some requested for removal of the device.

No previous studies have examined the correlation between age, parity, and vaginal discharge with the duration of IUD usage. However, some studies have shown its association indirectly.

The duration of IUD usage is strongly correlated with users' knowledge, attitude, and behaviour regarding IUD. Epidemiological studies demonstra-

ted that IUD is not popular among women in early adulthood.[17-19] Fleming et al discovered that only half of women in early adult hood knew about IUD.[18] Further analysis showed a significant correlation between parity and the willingness to use IUD. A study conducted by Zjil et al found that those with prior knowledge on IUD were still afraid to IUD. Infection and vaginal bleeding were noted to be the side effect from IUD.[11] Studies have also showed that good promotion could increase willingness in using IUD by 2.7 times.[9]

Health promotion and campaign to increase willingness to use IUD is still needed. Regarding to our findings, the promotion should be focused and addressed to women aged less than 30 and older than 35 years. Furthermore, the promotion should include information of efficacy, safety, and side effect of IUD.

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Research Article

Modification of Immediate Postplacenta CuT-380A IUD Insertion Using Ring Forceps and Standard Inserter: Twelve Months Follow-up

Modifikasi Teknik Insersi IUD CuT-380A Pascaplasenta Menggunakan Ring Forceps dan Inserter Standar: Pemantauan Dua Belas Bulan

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Abstract

Objective: To evaluate the outcome of CuT-380A IUD postplacental insertion in vaginal delivery using new modification insertion technique.

Method: We carried out a prospective cohort study of postplacental IUD insertion by means of 'push and push' technique, using ring forceps and standard inserter (inserter tube and plunger rod). We included women who underwent vaginal delivery from 1st June 2009 until 31st March 2011 and had postplacental IUD insertion. Follow-up was conducted for 12 months, including history, physical examination, ultrasound and questionnaires during evaluation, through home visits and by phone. The first monitoring is before 6 weeks after delivery, the second monitoring was after 6 weeks up to 3 months, the third is after 3 months up to 6 months, the fourth is after 6 months up to 12 months, the fifth is after 12 months up to 24 months and the sixth is after 24 months up to 32 months after insertion.

Result: On the second monitoring, 2 acceptors experienced expulsion. At the third monitoring period, one acceptor requested for IUD removal. At 9 months up to 12 months post-insertion, one expulsion was encountered, and one acceptor requested removal of device. At ≥12 months there was one acceptor who had IUD removal. We did not find any report of unintended pregnancy or perforation.

Conclusion: Immediate post-placental insertion of CuT-380A IUD after vaginal delivery using 'push and push' technique is safe and effective. The pregnancy rate at typical use is 0%, continuation rate is 94.1% and low expulsion rate (2.86%). Loss of follow up was 5.6% and no perforation was reported.

[Indones J Obstet Gynecol 2015; 2: 85-93]

Keywords: continuation rate, immediate post-placental IUD insertion, 'push and push' technique, typical use, vaginal delivery

Abstrak

***Tujuan**: Mempelajari luaran insersi IUD CuT-380A pascaplasenta persalinan pervaginam menggunakan teknik modifikasi baru 'push and push'.*

***Metode**: Kami melaksanakan studi kohort prospektif, sampel adalah semua ibu yang menjalani persalinan pervaginam pada 1 Juni 2009 sampai dengan 31 Maret 2011. Pemantauan dilakukan selama 12 bulan, yang meliputi anamnesis, pemeriksaan fisik, USG dan kuesioner saat kontrol, yang dilakukan melalui kunjungan rumah dan melalui telepon. Pemantauan dilakukan pada periode <6 minggu setelah persalinan, 6 minggu s/d 3 bulan, 3 bulan s/d 6 bulan, 6 bulan s/d 9 bulan, 9 s/d 12 bulan; dan lebih dari 12 bulan pascapersalinan.*

***Hasil**: Pada pemantauan periode 6 minggu sampai dengan 3 bulan pascapersalinan terdapat 2 akseptor yang mengalami ekspulsi. Pada pemantauan periode 3 bulan sampai dengan 6 bulan terdapat 1 akseptor yang meminta pencabutan IUD. Pada pemantauan periode 9 bulan sampai dengan 12 bulan, terdapat 1 kejadian ekspulsi dan 1 pencabutan IUD. Pada pemantauan setelah 12 bulan terdapat 1 pencabutan IUD. Tidak ada laporan kejadian perforasi maupun kehamilan.*

***Kesimpulan**: Insersi IUD pascaplasenta menggunakan teknik 'push and push' ditemukan aman dan efektif. Kehamilan pada penggunaan tipikal 0%, angka kelangsungan tinggi (94,1%) dan angka ekspulsi rendah (2,86%). Loss to follow up sebanyak 5,6% dan tidak ditemukan kejadian perforasi.*

[Maj Obstet Ginekol Indones 2015; 2: 85-93]

***Kata kunci**: angka kelangsungan, IUD pascaplasenta, penggunaan tipikal, persalinan pervaginam, teknik 'push and push'*

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INTRODUCTION

Postpartum IUD insertion was first performed by Liss and Andros (1963). Insertion was performed at 2-8 days postpartum, mostly on day four postpartum. Insertion technique utilizes a vaginal speculum, tenaculum and special inserter. The next year, Burnhill and Birnberg introduced Birnberg's bow insertion immediately after placenta delivery by using two fingers without use of a special inserter. In 1966, The International Postpartum Family Planning Program of the Population Council initiated a multicentre study where IUD insertion was performed before patients were discharged from the hospital, usually within 10 days after de-

livery. Overall expulsion rate of 20.5 per 100 women was obtained at 3 months follow-up. Expulsion rate was in the range of 7.35% to 46.2%.[1]

Sutopo et al performed insertion using type D and C Lippes Loop IUD at seven days postpartum, mostly on the first and second day of postpartum. Insertion was performed without a vaginal speculum, instead utilizing the index finger inserted into the cervical canal and the middle finger in the posterior or lateral fornix to immobilize the cervix. IUD was inserted using a special inserter (length 30 cm, diameter 5 mm). Among the 1,945 women, the expulsion rate was 10.8%. Highest expulsion incidence occurred in the first 3 months after insertion (7.7%), whereas at 3-6 months post-insertion the rate of expulsion was 1.5%.[2]

Sitompul et al demonstrated ML-Cu250 IUD insertion by holding the device between the index and middle finger, placed as high as possible in the uterine cavity, immediately inserted after delivery of the placenta. Results of 3 months monitoring showed expulsion rate was 7.1% from the 75 acceptors with loss of follow-up rate being 40%.[3]

Timing of IUD insertion can be classified as immediately or less than 10 minutes after delivery of the placenta (immediate postplacental insertion or IPPI), 48 hours postpartum (immediate postpartum), 4-8 weeks postpartum (late postpartum insertion) and interval insertion. Interval insertion is still widely chosen because of the low expulsion rate (3-13%) in comparison to IPPI (9.5 to 12.5%) and IPP (25-37%). Late postpartum insertion is not recommended due to the high rates of expulsion and perforation.[1,4,5] Nevertheless, postpartum insertion, especially immediate postplacental insertion, is superior to the interval insertion since it can reach acceptors as soon as possible since they already have had the device inserted when leaving the health facility, causes the patient very minimal pain because the cervix is still widely dilated, and is less expensive.[4,5]

In accordance with the practical guideline in normal birth management, active management of third stage of labor includes intramuscular injection of one ampoule oxytocin within the first minute after the baby is delivered in order to produce uterine muscle contraction immediately, preventing postpartum bleeding and reducing blood loss.[6] When applying this guideline, IUD insertion immediately after delivery of the placenta using the fingers tend to be difficult due to onset of myometrial contractions soon after the baby is born. Inserting the fingers and palm of the hand into the uterine cavity can prove to be hard and very uncomfortable for the mother.[7] To reduce the incidence of expulsion, in addition to IUD insertion training and clinical experiences in inserting IUD, it is important to place the IUD as high as possible in the fundus (high fundal placement).[1,5,8]

A postplacental IUD insertion method introduced by Hary Tjahjanto called the 'push and push' technique has been implemented in Kariadi Hospital since June 2009. This technique is a new modification of the existing postplacental IUD insertion technique, using a combination of ring forceps and standard inserter (standard inserter tube and plunger rods), so that the IUD can actually be placed in the middle of the uterine fundus although the cervical canal has been narrowed due to uterine contractions.[7]

METHODS

This study was conducted at Kariadi Hospital, a tertiary referral and teaching hospital for obstetrics and gynecology in Central Java. Our study was conducted prospectively, including all women who underwent vaginal delivery during the period of 1st June 2009 to 31st March 2011 that met the inclusion criteria, agreed to have immediate postplacental CuT-380A IUD insertion, and completed 12 months of monitoring. Inclusion criteria include all women who underwent vaginal delivery (spontaneous, with vacuum extraction or manual aid) who were willing to come to the clinic and undergo ultrasound monitoring according to the specified monitoring schedule. Whereas, exclusion criteria were women with sexually transmitted diseases/ AIDS, gynecologic malignancy, uterine anatomic abnormalities and women who do not require immediate contraceptives, including those with primary infertility, stillbirth or IUFD.

Insertion Method

IUD insertion was performed by the researchers and trained residents. The IUD string was cut at approximately 6 cm from the end of the vertical stem or in the middle of a long string. Afterwards, the string and vertical stem is inserted into the IUD inserter, but the horizontal arm remains outside the tube inserter. The plunger rod is inserted into the inserter tube and the inserter tube is clamped

with the horizontal arm in line with the tip of the ring forceps, or slightly lower than the outer edge of ring forceps tip (See figure 1). After the index and middle fingers enters the vagina, both ends of the fingers should be advanced through the lower uterine segment to reach the fibromuscular junction of the uterine corpus. Using the left hand to hold the ring forceps, the ring forceps is inserted gradually guided by the palm of the hand, onwards between the index and middle finger of the right hand until reaching the fibromuscular junction. After the ring forceps has been advanced maximally into the uterine cavity, the ring forceps is maintained in position using the first, fourth and fifth fingers of the right hand (See figure 2) while pressing the fundus using the left hand, so that the tip of the ring forceps slightly moves forward in the uterine cavity. The left hand is then used to push the ring forceps further into the uterine cavity, while the fingers of the right hand directs and maintains the position of the ring forceps. The left hand then presses the fundus again, advancing the ring forceps further into the uterine cavity. The process is repeated until the end of the ring forceps reached the fundus and the pressure is felt by the left hand upon palpation of the uterine fundus through the abdominal wall. Afterwards, with the left hand holding the inserter, the ring forceps is opened for 1-2 cm using the right hand, and the inserter tube is pushed to allow the tip of the ring forceps to be more attached to the wall of the uterine fundus. While maintaining inserter position using the left hand, ring forceps is removed and the inserter tube is pushed again so that the inserter tip moves into the narrow gap between the anterior and posterior uterine fundus wall, in conjunction with fundus control using the left hand. With the plunger rod held by the right hand, the inserter tube is withdrawn so the proximal end of the tube touches the ring of the plunger rod. Then the plunger rod is pulled out of the inserter tube, followed by pulling out the inserter tube from the uterine cavity. Thus, in addition to the ring forceps gradually entering the uterine cavity, insertion is done by pushing the ring forceps and standard inserter three times to place the IUD right in the center of the uterine fundus. Firstly when the ring forceps and inserter is inserted into the uterine cavity and later gradually driven to reach the fundus. Then, when the ring forceps was opened, the inserter is encouraged to move in the gap of the fundus wall; and after the ring forceps are removed from the uterine cavity, the inserter is advanced further so that the tip of the ring forceps is more attached to the walls of the uterine fundus. Advancement of the ring forceps or tube inserter must be accompanied by fundus palpation on the abdominal wall with the left hand to ensure the position of the ring forceps tip right in the centre of the fundus and to prevent perforation.

Figure 1. How to Place the IUD in the Inserter Tube and Clamped with the Ring Forceps.

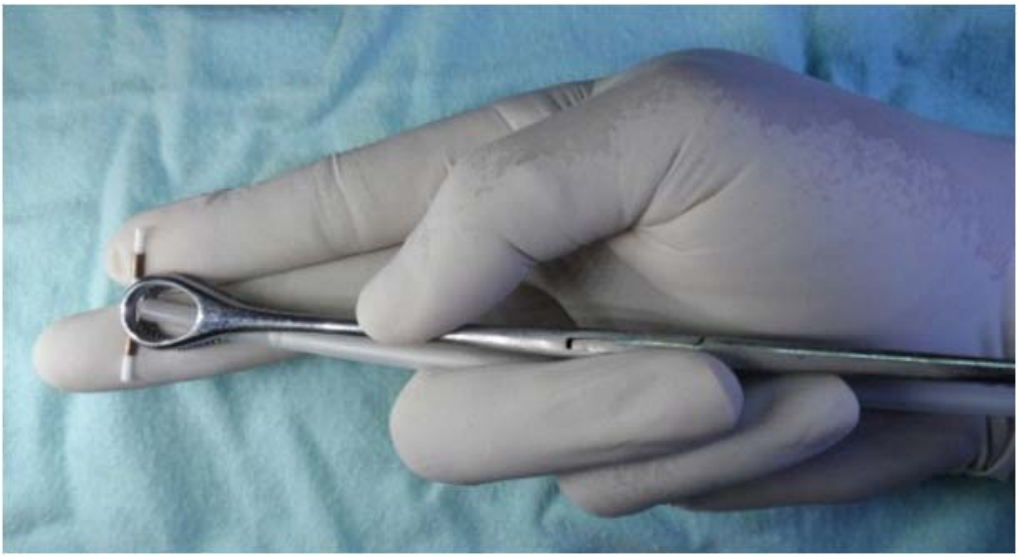

Figure 2. How to Use the First, Fourth and Fifth Fingers of the Right Hand to Hold the Ring Forceps.

IUD insertion was not limited to the first 10 minutes after delivery of the placenta. Insertion is done when the uterine cavity has been confirmed to be clean of blood clots and any amniotic tissue. This is done to reduce the risk of expulsion, especially during puerperal period. In addition to requiring the uterine cavity to be in a clean state, uterine tonic contractions is also needed to reduce the risk of expulsion by administering intramuscular injection of one ampoule of oxytocin after the baby is born. If no contraindications were present, methylergometrine maleate was also given through intramuscular or intravenous injection during or after delivery of the placenta. In women with weak uterine contractions or at risk for weak uterine contraction in the third stage of labor; for example women who were multigravida, or had severe preeclampsia or typhoid fever or hepatitis; 600-800μg of misoprostol was administered per rectal as additional uterotonic agents. Furthermore, to ensure maintenance of uterine involution, methylergometrine maleate tablets were administered (½-1 tablet, three times daily for 1-2 weeks).

Follow-up Schedule

At the first follow-up visit, within 6 weeks postpartum, routine gynecological examination was performed to assess the presence of excessive bleeding complications, partial or complete expulsion, and perforation through pelvic examination. Transvaginal or abdominal ultrasonography of the pelvis was performed to determine the position of the IUD. At the second (6 weeks up to 3 months postpartum), third (3 up to 6 months postpartum), fourth (6 up to 9 months postpartum), fifth (9 up to 12 months postpartum) and sixth (more than 12 months) monitoring visits, abdominal ultrasound examination was performed and IUD string was cut when necessary. Furthermore, presence of side effects and continuation of IUD use was evaluated. When acceptor did not present within the predetermined schedule, interview by phone, written letter or home visit was performed. If the patient could not be contacted until the end of the study, they were considered lost to follow-up.

The parameters studied were efficacy, incidence of complications related to IUD use and continuation rate. Data were recorded in a special form and analyzed descriptively.

RESULTS

From 1st June 2009 until 31st March 2011, 431 postplacenta IUD insertions were carried out. At the end of the study, the number of women who were observed and have been using an IUD for 12 months or more was 108 mothers. The number of acceptors that can be monitored for 12 months is 102 acceptors of IUD acceptors. Thus, lost to follow-up is 5.6%.

Table 1. Monitoring Data

	M-1	M- 2	M-3	M-4	M-5	M-6
Acceptor	108	108	108	108	108	108
Observation						
Visit	23 (21.3%)	18 (16.7%)	4 (3.7%)	2 (1.8%)	9 (8.4%)	26 (24.1%)
By phone	29 (26.8%)	25 (23.1%)	36 (33.3%)	8 (7.4%)	15 (13.8%)	76 (70.3%)
Total observed	52 (4.1%)	43 (39.8%)	40 (37.0%)	10 (9.2%)	24 (22.2%)	102 (94.4%)
Loss to follow-up	56 (51.9%)	65 (60.2%)	68 (63.0%)	98 (90.8%)	84 (77.8%)	6 (5.6%)

Note: *M-1 = up to 6 weeks postpartum, M-2 = 6 weeks up to 3 months postpartum, M-3 = 3 up to 6 months postpartum, M-4 = 6 up to 9 months postpartum, M-5 = 9 up to 12 months postpartum, M-6 = 12 months postpartum or later.*

The most commonly encountered age group amoung the acceptors was 30-34 years old (27.1%), with the youngest being 17 years old and the oldest being 42 years old. The proportion of preterm delivery was only 6.7%, while the rest were full-term and post-term deliveries (93.4%). The proportion of primipara and multipara was almost equal. The average body mass index was 19.92. Almost all of the babies' birth weight was in the range of 2,500-3,999 grams. Three-quarters of the deliveries were spontaneous labor. As many as 15 acceptors (13.9%) had premature rupture of membranes at the time of delivery (Table 2).

Table 2. Patient Characteristics

Variable	n	Proportion (%)	Mean (SD)	Min	Max
Age (years)			27.41	17	42
15-19	10	9.3			
20-24	28	26.2			
25-29	28	26.2			
30-34	29	27.1			
≥ 35	12	11.2			
Normotension	92		119.95 (7.129)	100	130
Hypertension			157.14 (13.828)	140	180
140-160 mmHg	11	10.2			
>160 mmHg	3	2.8			
BMI *)	85		25.93 (3.40)	19.92	39.54
Gestational age (weeks)			38.74 (1.95)	30	42
Preterm	7	6.6			
Full term	95	90.5			
Post-term	3	2.9			
Parity			1.69 (0.79)	1	4
Primipara	52	48.6			
Multipara	55	51.4			
PROM					
No	93	86.1			
Yes, < 6 hours	10	9.3			
Yes, > 6 hours	5	4.6			

Variable	n	Proportion (%)	Mean (SD)	Min	Max
Birth weight (gr)			2,995 (382)	1,800	4,250
<2500	7	6.5			
2500-3999	100	92.6			
>4000	1	0.9			
Mode of delivery					
Spontaneous	81	75			
Vacuum extraction	25	23.1			
Breech delivery	2	1.9			
Haemoglobin (g%)			11.06 (1.31)	7.1	13.9
<8	2	2.1			
8-10	15	15.6			
10-12	53	55.2			
≥ 12	26	27.1			

BMI = Body Mass Index, PROM = premature rupture of the membrane
**) n = number of samples for which data is complete*

As many as 52 acceptors were observed on the first monitoring with no complaint of smelly lochia, but 5.8% reported having experienced a period of fever after childbirth. Complaints of vaginal discharge, pelvic pain, painful menstruation, and excessive menstrual blood were also reported by some acceptors but did not lead to request for IUD removal (Table 3).

Table 3. Patient Complaints at Each Monitoring Period.

	M-1 (n=52) (%)	M-2 (n=43) (%)	M-3 (n=40) (%)	M-4 (n=10) (%)	M-5 (n=24) (%)	M-6 (n=102) (%)
Smelly lochia						
• No	52 (100)					
• Yes	--					
Vaginal discharge						
• No		30 (69.8)	37 (92.5)	7 (70)	23 (95.8)	81 (79.4)
• Yes		13 (30.2)	3 (7.5)	3 (30)	1 (4.2)	21 (20.6)
Puerperal fever						
• No	49 (94.2)					
• Yes	3 (5.8)					
Pelvic discomfort						
• No	52 (48.1)	42 (97.7)	40 (100)	10 (100)	24 (100)	93 (91.2)
• Yes	56 (51.9)	1 (2.3)	--	--	--	9 (8.8)
Dysmenorrhea						
• No		10 (83.3)	39 (97.5)	7 (77.8)	17 (73.9)	55 (53.9)
• Yes		2 (16.7)	1 (2.5)	2 (22.2)	6 (26.1)	47 (46.1)
Menstrual bleeding						
• Normal		12 (100)	40 (100)	9 (100)	22 (95.7)	100 (98.0)
• Menorrhagia		--	--	--	1 (4.3)	2 (2.0)

Table 4. Timetable of Expulsion, IUD Removal and Cummulative Continuation Rate (n=102).

	M-1	M-2	M-3	M-4	M-5	M-6
Expulsion	0	2 (1.96%)	2 (1.96%)	2 (1.96%)	3 (2.86%)	3 (2.86%)
Removal						
• medical	0	0	1 (0.98%)	1 (0.98%)	1 (0.98%)	2 (1.96%)
• pregnancy	0	0	0	0	0	0
• personal	0	0	0	0	1 (0.98%)	1 (0.98%)
Continuation rate	102 (100%)	100 (98.04%)	99 (97.06%)	99 (97.06%)	97 (95.09%)	

At the final follow-up visit (more than 12 months) 94.4% of acceptors were observed. Cummulatively, we encountered three occurences of IUD expulsion (2.86%) and three removals (2.94%), two were removed due to medical reasons (1.96%) and one acceptor (0.98%) cited personal reasons. Thus, the continuation rate was 94.2%.

DISCUSSION

A major problem in postplacental IUD insertion is the high expulsion rate in comparison to interval insertion. High rates of expulsion is influenced by timing of insertion and the method of IUD insertion.[8,9] A cohort study by Stumpf and Lenker involving 114 women, using modified Lippes Loop IUD found that at 6 months post-insertion expulsion rate was 30%; and compared to ring forceps insertion; most expulsions occurred in the digital insertion group. They concluded that the modified form of IUDs does not influence the risk for expulsion, but it is instead affected by the IUD insertion technique.[8]

A Cochrane review in 2010 included a multicentre study by WHO involving 841 women as samples. Comparison of the Nova-T-PP, Lippes Loop D, and Copper 7, indicated that the Lippes Loop was likely to be inferior to the other two devices. The 12-month discontinuation rates due to expulsion per 100 women were 41.3 for the Nova-T-PP, 44.1 for the Lippes Loop, and 34.8 for the Copper 7. The corresponding 12-month pregnancy rates showed that Lippes Loop had the highest pregnancy rate with 12.1 per 100 women. Total 12-month discontinuation rates were high with all devices; 53.1, 60.9, and 47.7 per 100 women for Nova-T-PP, Lippes Loop D, and Copper 7, respectively. The discontinuation rate at 12 months was significantly higher for the Lippes Loop than for the Copper 7. A study by Thiery et al included 562 women receiving either TCu-200 or MLCu-250 IUDs, who were observed for 12 months. Expulsion rates were 9.9% and 11.2% and pregnancy rates were 2.4% and 0.5%, respectively. Lavin et al observed 400 women receiving Progestasert IUD or TCu-200 IUD for 12 months. Expulsion rates were 35.8% and 9.0% with hand insertions, and 35.2% and 8.1% with ring forceps insertion, respectively. A multicenter study by Family Health International study included a total subject of 3,797 women from 13 countries. Expulsion rate of Delta Loop IUD inserted by hand or using ring forceps were comparable % at 6 months monitoring.[9]

Apello et al observed 400 women for 12 months. Expulsion rate of TCu-200 IUD and Progestasert by hand insertion were 19.9% and 39.0%, respectively. While insertion using instruments found expulsion rate to be 10.3% and 14.2%, respectively. Kisnisci et al discovered expulsion rate of Delta-T IUD was 7.6% and 3.7% for Delta Loop, but the insertion method was not mentioned.[9,10]

Van Kets et al included 408 women with an 18-months monitoring period; and found that expulsion rates for postpartum Nova-T (Nova-T-PP) and Nova-T were 6.2% and 6.6%, respectively. Continuation rate at 12 months of Nova-T-PP and Nova-T were 67.2% and 70.2%, respectively; and pregnancy rates were 0.6% and 0% respectively. This indicates that expulsion rate between the two IUD models did not differ significantly, suggesting that the addition of two extra arms to the original Nova-T model does not improve the retention of the adapted IUD model.[11]

Xu et al observed 910 women using CuT-380A IUD through a 12-months follow-up period, and discovered that the expulsion rate was comparable between hand insertion and insertion using instrument.[12] Chen et al compared immediate and delayed (post-puerperal) insertion of LNG-IUS, and

obtained expulsion rates of 23.5% and 13.7% at 6 months monitoring, respectively.[13]

We identified two postpartum IUD insertion studies in Indonesia. Soetopo et al studied LL type C and D IUD Insertion performed on day one or two post-partum, and obtained an expulsion rate of 10.8%.[2] Meanwhile, Sitompul et al observed digital insertion of MLCu250 IUDs. At 3 months monitoring, the expulsion rate was 7.1%.[3]

Kariadi Hospital applied the 'push and push' technique and obtained expulsion rate of 2.86% during 12-months follow-up. This technique uses ring forceps and standard IUD inserter (tube inserter and plunger rod). Insertion is performed using a blind method, without use of a vaginal speculum. Using the middle and index finger as a guide to reach the uterine cavity, and by using ring forceps to enter the cervical canal more easily, we were able to place the IUD at the center of the uterine fundal wall. A standard inserter can aid in inserting the IUD as close as possible to the fundal wall and prevent the occurrence of position changes when the ring forceps was pulled out of the uterine cavity. Insertion time is not limited to the first 10 minutes after placenta delivery but it was more preferable to have the uterine cavity to be clean of blood clots and amniotic tissue. By using ring forceps to clamp the inserter tube, the inserter tube can be advanced through the internal cervical os, although the internal cervical os has narrowed. After the ring forceps reaches the fibromuscular junction, it is then gradually pushed into the uterine cavity.

Prospective cohort study by Morrison et al, 1996, in Mali (n = 224) and Kenya (n = 110), during 6 months monitoring, performed immediate CuT-380A IUD insertion and late insertion by hand and ring forceps. In Kenya, 71% had immediate insertions and 80% of the insertions were made using ring forceps. In Mali, 54% of acceptors had immediate insertions and 57% of insertions were performed by hand. Only four expulsions occurred among the 219 participants completing a follow-up visit in Kenya (1.8%). In Mali, 19 expulsions (including 15 displacements) occurred among the 98 participants with complete follow-up information (19.4%).[14]

A non-randomized clinical trial by Eroglu et al involved 268 women who had vaginal or cesarean delivery in whom CuT-380A IUD insertion were performed either immediately postplacenta (IPP; up to 10 minutes postpartum), during early postpartum (EP; more than 10 minutes but less than 72 hours after delivery), during the interval period (INT; more than 6 weeks after vaginal delivery or more than 8 weeks after cesarean section. At 1 year follow up, complete expulsion occurred in 14.3% of the women in the IPP group, in 18.6% of the EP group, and in 3.8% of the INT group. Partial expulsion was encountered in 22.6% of the women in the IPP group, in 51.2% of the EP group, and in 3.1% of the INT group. There was a statistically significant difference in regards to the occurrence of complete or partial expulsion based on the time of IUD insertion ($p<0.001$).[15]

A Cochrane review in 2010 stated that the immediate post-placental insertion (IPPI) is generally safe and effective, with expulsion in IPPI higher than delayed insertion. It also found that modified forms of IUD does not improve the expulsion rates. Moreover, digital insertion and insertion using instrument had similar success, with experience found to be an important factor in reducing expulsion.[9,16]

Celen et al conducted a prospective cohort study assessing the effectiveness of postplacental CuT-380A IUD insertion using a ring forceps in vaginal and cesarean deliveries. They obtained an expulsion rate of 12.3% and 2 pregnancies occurring among the 235 acceptors within 1 year of IUD use (0.7%).[17]

An RCT by Beltagy et al observed the insertion CuT-380A and MLCu-375 IUD within 48 hours after a normal delivery using Kelly forceps, with each group comprised of 150 women. Evaluation included ultrasound examination at 6 weeks and 6 months post-insertion. The expulsion rates for both groups were comparable (14.9% for CuT-380A vs 15% for MLCu-375). A relationship was identified between the distance of the IUD to the endometrium and the occurrence of expulsion, with the cut-off point of 10 mm.[18]

Several studies stated that there was no incidence of perforation with IPPI.[9,14,15] In our study, there was no incidence of perforation. To prevent perforation, it is essential that the left hand controls the uterine fundus during each time the ring forceps or inserter are advanced into the fundus.

CONCLUSION

In 12 months follow up, there is no occurrence of pregnancy in all 102 acceptors and the number of women who are still using the IUD total of 96 women. So the Pearl index was 0, or 0% typical use, and the continuation rate is 94.2%. Expulsion rate by 2.86% and no incidence of perforation. Thereby can be concluded that immediate post-placental IUD insertion using push and push technique is safe, convenient and high effectiveness.

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Research Article

Factors Affecting Selection of Contraceptive Methods and Its Length of Use

Faktor-Faktor yang Mempengaruhi Pemilihan Jenis Kontrasepsi dan Lama Pemakaiannya

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Abstract

Objective: To evaluate the factors related to the selection of contraceptive methods and length of use on acceptors in Raden Saleh Clinic and Fatmawati General Hospital.

Method: The study was a prospective observational study designs. The factors that we observed include the family planning factor (wife age, number of desired children and infertility), subjective factors (side effect experience of contraception, support from the husband/family, and religion), objective factors (medical disorders, person helping to select contraception, family planning service centre and availability of contraceptives) and the level of motivation (level of education). All the clients who will receive contraception and meet the criteria for the research were interviewed and given questionnaires until the desired sample size is achieved. The study was conducted at the Raden Saleh Clinic and Fatmawati General Hospital. We then conducted follow-up at 3 and 6 months after the use of the contraceptive methods to assess the length of use.

Result: The total number of subjects was 151 people. The average age of respondents was 31 years old, with the contraception options being IUD (67.1%), implants (17.8%), sterilization (7.2%), injectable contraception (3.9%), and oral contraception (3.9%). From all the factors studied, only the number of desired children were found to affect the selection of contraceptive methods significantly (p=0.008) in Fatmawati General Hospital, while in Raden Saleh Clinic all of the factors did not affect the selection of contraceptive method (p>0.05). We also found that all of these factors do not have a significant relationship to the length of contraceptive use (p>0.05). There were 6.6% of subjects (n=10) who switched the type of contraception. From all of them, there was a trend of switching from oral contraceptive to injectable method (33.3%) and from IUD to injectable method (66.7%).

Conclusion: Only the number of desired children has an effect on the selection of contraceptive methods in Fatmawati General Hospital, while in Raden Saleh Clinic all of the factors studied do not affect in selection of contraceptive methods. Family planning factors, subjective factors, objective factors and motivation levels have no effect on the length of contraceptive use by clients at Raden Saleh Clinic and Fatmawati General Hospital.

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Keywords: contraception methods, factors, length of use, selection

Abstrak

***Tujuan**: Meneliti faktor-faktor yang mempengaruhi pemilihan jenis kontrasepsi dan lama pemakaiannya pada akseptor KB di Klinik Raden Saleh dan Rumah Sakit Umum Pusat Fatmawati.*

***Metode**: Studi ini adalah penelitian observasional dengan desain prospektif. Faktor yang diteliti meliputi faktor perencanaan keluarga (usia istri, jumlah anak yang diinginkan dan infertilitas), faktor subjektif (pengalaman efek samping kontrasepsi, dukungan suami/keluarga dan agama), faktor objektif (gangguan medis, yang membantu memilih kontrasepsi, tempat layanan kontrasepsi dan ketersediaan alat kontrasepsi) dan tingkat motivasi (tingkat pendidikan). Semua klien yang akan menerima kontrasepsi dan memenuhi kriteria penelitian, diwawancara dan diminta mengisi kuesioner hingga mencapai jumlah sampel yang diinginkan. Penelitian dilakukan di Klinik Raden Saleh RSCM dan RSUP Fatmawati. Kemudian dilakukan follow up pada 3 dan 6 bulan pasca menerima kontrasepsi untuk menilai lama pemakaiannya.*

***Hasil:** Jumlah total subjek sebanyak 151 orang. Rata-rata usia responden 31 tahun dengan pilihan jenis kontrasepsi AKDR 67,1%, implan 17,8%, kontap 7,2%, suntik 3,9% dan oral 3,9%. Dari seluruh faktor yang diteliti, hanya faktor jumlah anak yang diinginkan yang terbukti secara statistik berpengaruh dalam pemilihan jenis kontrasepsi (p=0,008) di RSUP Fatmawati, sedangkan di Klinik Raden Saleh semua faktor tersebut tidak terbukti secara statistik berpengaruh dalam pemilihan jenis kontrasepsi (p>0,05). Didapatkan pula bahwa seluruh faktor tersebut juga tidak memiliki pengaruh secara statistik (p>0,05) terhadap lamanya pemakaian kontrasepsi, baik di Klinik Raden Saleh maupun di RSUP Fatmawati. Dari 6,6% subjek (n=10) yang mengganti jenis kontrasepsi, terdapat kecenderungan perubahan jenis kontrasepsi dari oral menjadi suntik (33,3%) dan AKDR menjadi suntik (66,7%).*

***Kesimpulan**: Faktor jumlah anak yang diinginkan memiliki pengaruh dalam pemilihan jenis kontrasepsi di RSUP Fatmawati, sedangkan di Klinik Raden Saleh semua faktor yang diteliti tidak berpengaruh dalam pemilihan jenis kontrasepsi. Faktor perencanaan keluarga, faktor subjektif, faktor objektif dan tingkat motivasi tidak memiliki pengaruh terhadap lamanya pemakaian kontrasepsi pada klien di Klinik Raden Saleh dan RSUP Fatmawati.*

[Maj Obstet Ginekol Indones 2015; 2: 94-99]

***Kata kunci**: faktor-faktor, jenis kontrasepsi, lama pemakaian, pemilihan*

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INTRODUCTION

Indonesia is a large country with the fourth biggest population in the world after China, India and United States. According to the 2010 demographic survey published by the Central Bureau of Statistics Depatment in August 2010, the Indonesian population amounted to 237,556,363 people.[1] If this population growth is not controlled, it will cause many problems in the future. Indonesia's population will reach 273 million by the year 2025 if the family planning program does not work well.[2] This condition would complicate the government's efforts in improving the welfare of the people. It can also cause serious problems in the economic, social, political, cultural, and security sectors, which will impact the health situation. Therefore, family planning services held by the government of the Republic of Indonesia are currently focusing on avoiding population explosion in the future.[2] Based on Riskesdas 2013, the prevalence of family planning in Indonesia is 59.3%, with 51.8 % using hormonal contraception and 7.5% using non-hormonal contraception.[3]

Counseling is an important aspect in family planning and reproductive health services.[4] By doing counseling, we are able to assist clients in selecting and deciding the type of contraception that will be used in accordance with their choice. Based on many literatures, there are 4 factors that influence the client in choosing a contraceptive method, they are family planning factors (wife age, number of desired children, the frequency of intercourse and infertility), subjective factors (previous experience with contraceptive methods, effectiveness, contraception side effect, the support of husband/family, religion, and costs), objective factors (consideration of medical issues, the competence of health care providers, the availability of contraception, menstrual history, family history, physical examination, and pelvic examination) and the motivation level (level of education, level of prosperity, and lifestyle).[5-8] All of these factors will also affect the success rate of family planning programs.

Based on the research by Budi Palarto and Radita Kusumaningrum on childbearing aged couples in the Batang district, Central Java, they obtained that wife age, number of children, and level of education had a significant relationship with the choice of contraception, while the family welfare level factors, the ownership of Jamkesnas, level of knowledge, spousal support and influence of religion does not have a meaningful relationship. From all of those factors mentioned above, wife age is the most influential factor in choosing the contraceptive methods.[9] However, so far there are no research on factors related to the length of contraception use among the acceptors.

METHODS

We performed a prospective observational study aimed to determine the factors that influence the choice of contraception and its duration of use in Raden Saleh Clinic and Fatmawati Hospital in December 2013 to December 2014. The factors studied were grouped into four, they are the family planning factors (the wife age, the number of desired children and infertility), the subjective factors (previous experience with contraception side effects, support from the husband/family and religion), the objective factors (medical problems, the person helping in choosing contraception, place of contraceptive services and the availability of contraceptive methods), and the motivation level (education level).

The inclusion criteria in this study is women aged 18-45 years old who came to Raden Saleh Clinic and Fatmawati general hospital to get contraception. She can choose one of the existing contraception methods with equal probability and willing to participate in this study. The subjects were then followed until 3 and 6 months after using the contraception. All the clients who were willing to fill out a questionnaire, but were not reachable for follow-up after getting contraception were considered as dropouts.

Data was recorded and stastitical analysis was performed using SPSS version 17.

RESULT

During the study period we successfully recruited total of 152 subjects consecutively, 65 subjects in Raden Saleh Clinic and 87 subjects in Fatmawati general hospital. Then we conducted follow-up at 3 months and 6 months after using the contraception methdos. At the first follow-up we discovered that 151 subjects were still using their chosen contraceptive methods and there was 1 subject who dropped out due to loss of contact (the provided

phone number was not active and she already moved to the another province). At second follow-up we found that 142 subjects still used the same contraceptive methods they initially chose.

In this study, the average age of our subjects was 31.38 years old, with 71.5% of them having graduated from middle education level (junior-senior high school). Almost 90% of the subjects are Muslims, which constitute as the majority religious belief in Indonesia. The selection of contraceptive methods were mostly recommended by midwives or their husbands (85.4%). A total of 66.9% subjects chose Intra Uterine Device (IUD) as their contraceptive of choice. The reasons for using this method are to prevent pregnancy or to regulate the interval between pregnancies. Meanwhile, 4% of the subjects chose sterilization since they do not want to have anymore children. We also discovered that 64.2% of the subjects wanted to have only two children.

Table 1. The Relation between the Factors with the Selection of Contraception Methods in Fatmawati General Hospital

Characteristic	Oral n (%)	Injection n (%)	Implants n (%)	IUD n (%)	Sterilization n (%)	p
Age of wife mean (SD), years	0 (0)	28.6 (5.3)	28.8 (5.4)	28.3 (5.6)	35.3 (5.29)	0.005[a]
Education level						
Low (no education -elementary)	0 (0)	1 (20.0)	2 (15.4)	2 (3.4)	1 (10.0)	0.461[b]
Middle (junior-senior high school)	0 (0)	3 (60.0)	11 (84.6)	50 (86.2)	9 (90.0)	
High (Diploma - University)	0 (0)	1 (20.0)	0 (0)	6 (10.3)	0 (0)	
Religion						
Moslem	0 (0)	5 (100.0)	13 (100.0)	56 (96.6)	10 (100.0)	1.000[c]
Christian	0 (0)	0 (0)	0 (0)	2 (3.4)	0 (0)	
Husband opinion/support						
Agree	0 (0)	5 (100.0)	13 (100.0)	57 (98.3)	10 (100.0)	N/A
Not Agree	0 (0)	0 (0)	0 (0)	1 (1.7)	0 (0)	
Person helping to choose contraception						
Midwife	0 (0)	0 (0)	2 (15.4)	16 (27.6)	3 (30.0)	0.206[c]
Husband and family	0 (0)	5 (100.0)	5 (38.5)	32 (55.2)	6 (60.0)	
Doctor (GP and Ob-gyn)	0 (0)	0 (0)	6 (46.2)	10 (17.2)	1 (10.0)	
Number of desired children						
1 child	0 (0)	1 (20.0)	1 (7.7)	2 (3.4)	0 (0)	0.001[b]
2 child	0 (0)	4 (80.0)	9 (69.2)	41 (70.7)	1 (10.0)	
> 2 child	0 (0)	0 (0)	3 (23.1)	15 (25.9)	9 (90.0)	
Medical problems						
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
No	0 (0)	5 (100.0)	13 (100.0)	58 (100.0)	10 (100.0)	
The duration of having the first child						
≤ 1 year	0 (0)	4 (80.0)	9 (69.2)	35 (60.3)	5 (50.0)	0.994[c]
> 1 year	0 (0)	1 (20.0)	4 (30.8)	23 (39.7)	5 (50.0)	
The experience of contraception side effects						
Yes	0 (0)	0 (0)	1 (7.7)	6 (10.3)	1 (10.0)	1.000[c]
No	0 (0)	5 (100.0)	12 (92.3)	52 (89.7)	9 (90.0)	
The availability of contraception methods						
Complete	0 (0)	5 (100.0)	13 (100.0)	58 (100.0)	10 (100.0)	N/A[*]
Not complete	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

[a]Anova test; [b]Kruskal-Wallis test; [c]Kolmogorov-Smirnov test; [*]cannot be analyzed

From this study, we found that in Raden Saleh Clinic and Fatmawati general hospital IUD is still the favorite choice of contraceptive method (66% and 67%, respectively), followed by the implant method as the second most frequent choice (23% and 15%, respectively). The sterilization method is more commonly encountered in Fatwamati general hospital than Raden Saleh Clinic (12% vs 2%, respectively). The role of the midwife and her husband or family in determining the type of contraception is very large, where most of them chose IUD as their preference.

From the eleven factors that influence the selection of contraception in Raden Saleh Clinic, we found no factor that were statistically significant in affecting their choice ($p>0.05$). In Fatmawati general hospital, the number of desired children had a statistically significant relationship with the selection of contraceptive methods ($p<0.05$), while the other factors were not statistically significant. Most of the subjects (n=140, 92.7%) chose to use contraception that still retained their fertility due to the desire of having more children.

We also found that the age of the wife, education level, religion, husband's opinions, the person who helped in selecting the contraceptive methods, the number of desired children, age when having the first child, medical problems, previous experience with contraception side effects, the availability of contraception, and the suitability of choice is not proven to be statistically significant ($p>0.05$) in influencing the duration of contraceptive use in both Raden Saleh clinic and Fatmawati general hospital. The tendency to use their contraceptive method for less than 6 months is higher for subjects in Raden Saleh clinic than in Fatmawati general hospital (70% vs. 30%).

We found 10 subjects (6.6%) who switched their contraceptive methods. The changes of contraceptive methods is presented in Table 2. From all of them, there is a tendency of switching from oral contraceptive to injection method (33.3%) and from IUD to injection method (66.7%).

DISCUSSION

In the effort of controlling the rate of population growth in Indonesia, family planning is one right way to cope with the population explosion in the future. Family planning programs can be done through traditional or modern ways. Traditional contraceptive methods include coitus interruptus and periodic abstinence,[10] while modern contraceptive methods include oral contraceptives, injectables, IUD, implants, condoms and lactation method.

From the 152 subjects recruited, there was one patient who was dropped out from this study due to loss of contact. The average age of our subjects was 31.38 years old. Most of subjects were recruited in Fatmawati general hospital (n=86). Based on educational level, the subjects mostly belonged in the category of middle education (junior-senior high school) and most of them were Moslem (90.7%). In this study, the husband mostly agreed with his wife having contraception (99.3%), where there was only one subject whose husband did not agree. The most common contraceptive method selected by the subjects was IUD (66.9%), followed by implants (18.5%). This is consistent with the results of the Indonesia Health Research in 2013, where the use of long-term contraceptive methods (IUD, implant, sterilization) has a higher distribution (49.1%) compared to the short-term contraceptive methods (10.2%).[3]

Table 2. The Changes in Contraceptive Methods

Previous contraceptive method	New contraceptive method							
	Oral		Injection		IUD		Didn't change	
	n	%	n	%	n	%	n	%
Oral	0	0.0	2	33.3	1	100.0	3	2.1
Injection	1	33.3	0	0.0	0	0.0	4	2.8
Implants	0	0.0	0	0.0	0	0.0	28	19.9
IUD	2	66.7	4	66.7	0	0.0	95	67.4
Sterilization	0	0.0	0	0.0	0	0.0	11	7.8

In helping clients choose the type of contraception in accordance to the client's condition, good counseling is necessary so that the client can use a contraceptive choice for longer and increase the success rate of contraception.[5] From the many factors that have been studied previously, this study only examined several factors, namely the family planning factors (the age of the wife, number of desired children, and infertility), the subjective factors (experience with contraception side-effects, support from the husband/the family, and religion), the objective factors (medical problems, the person helping in choosing contraception, the place of contraceptive services, and the availability of contraceptive methods) and the motivation level (education level).[6-9]

The median age of the subjects who chose the IUD was 31 years, while the median age of the subjects who chose contraceptive implant and sterilization were 32.5 years and 36 years, respectively. It can be seen that the age of subjects who chose sterilization is older than other contraceptive methods. The reasons of getting contraception in this study include preventing pregnancy (62.9%), adjusting the interval between pregnancies (26.5%), not wanting to have any more children (7.3%), and following the instructions of the midwife or doctor (3.3%).

At Raden Saleh clinic, the most commonly selected contraceptive method is IUD, followed by implant, oral contraceptives, and sterilization. Meanwhile, in Fatmawati general hospital the most preferred contraceptive method is IUD, followed by implants, injections and sterilization. It seems that IUD is still the most favourite contraceptive methos in both of the health care centers because of its high effectivity (99%).[11-13] The role of the midwife and husband/family in helping to select the contraceptive methods suitable for the client is very large, compared to general practitioners and specialists (Ob-Gyns) (85.4% vs. 14.6%). There were only 19 subjects (12.5%) who have experienced getting contraception previously. The side effects experienced by the subjects were menstrual disorders, vaginal discharge, acne and weight gain.[14,15]

After statistical analysis to connect the factors studied to the selection of contraception methods, we obtained that only the number of desired children carry an influence on the selection of contraceptive methods (p=0.008) in Fatmawati general hospital. Whereas in Raden Saleh Clinic, all of the factors studied had no significant effect (p>0.05) on the selection of contraception. This is consistent with research conducted by Kusumaningrum et al in Batang district in Central Java in 2008, which stated that the age of wife, the number of desired children and the level of education has a significant relationship with the selection of contraception, while the support of family and religion do not have a significant influence.[9] In this study, the age of the wife and educational level did not have a statistically significant influence on the selection of contraceptive method due to differences in the characteristics of the subjects and places. All of those factors do not affect the duration of contraceptive use, both in Raden Saleh Clinic and Fatmawati general hospital. So far, there has been no studies linking these factors to the duration of contraceptive use. This is possibly because the follow-up period is too short, so that the possibility of subjects switching their contraceptive methods is minimal. Furthermore, the contraceptive side effects are subjective, so it will differ in severity and time. Therefore, it requires further study with a larger sample size and a longer follow-up period to determine the factors that may influence the contraceptive use duration.

Nevertheless we found that in the Raden Saleh Clinic, there is a greater tendency to use contraception for less than 6 months than in Fatmawati general hospital because there are differences in subject characteristics and motivation in both of those centres. In Raden Saleh Clinic, clients receive contraception mostly after mentrual induction due to a variety of reasons; while at Fatmawati general hospital most of them had postpartum contraception, so it is reasonable that subjects would use their contraception longer.

From ten subjects who switched the method of contraception, two subjects replaced the contraceptive method at less than six months due to menstrual disorder and vaginal discharge, while the eight subjects who switched the type of contraception in the next 6 months also stated the same reasons. This study found a tendency of switching from oral contraceptives to injectable method (33.3%) and from IUD to injection (66.7%). The education level of the subjects who changed their contraceptive method is mostly basic education level (70%) and the rest was middle education level (junior-senior high school). This phenomenon can be explained by the lack of understanding on the benefit and importance of contraception to im-

prove the health of women and the low level of motivation for using contraception.

Good counseling to clients before receiving contraception will increase the level of understanding and motivation level of the importance of family planning, so that the client can determine the choice of contraceptive method in accordance with their preference. This will indirectly affect the duration of contraceptive use by the client.

CONCLUSION

In Fatmawati general hospital, we obtained that the number of desired children was confirmed to significantly affect the selection of contraceptive methods; whereas the age of wife, infertility, experience with contraception side effects, the support of husband/family, religion, medical problems, person helping to choosing contraception, the availability of contraception and education levels do not carry a significant influence in the selection of contraceptive methods. Meanwhile in Raden Saleh Clinic, all of the factors that we studied do not affect the selection of contraceptive methods.

All of the factors studied do not affect the duration of contraception use in either of the centres. There is a tendency for subjects in Raden Saleh Clinic to use their contraception for less than 6 months more often than in Fatmawati general hospital. There were subjects who switched their method from oral contraceptive to injection method and from IUD to injection.

Further studies with a larger sample size and longer follow-up period is needed in order to determine the factors influencing the duration of the contraceptive use.

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Research Article

Prevalence of Lower Urinary Tract Symptoms in Women Based on Bahasa Indonesia Validated ICIQ-FLUTS Long Form

Prevalensi Gejala Saluran Kemih Bawah pada Perempuan Berdasarkan ICIQ- FLUTS Long Form Tervalidasi Bahasa Indonesia

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Abstract

Objective: To obtain the prevalence of women with lower urinary tract symptoms (LUTS) in Dr. Cipto Mangunkusumo National Hospital, Indonesia.

Method: We conducted a descriptive and analytic study with questionnaire-based data collection. All subjects were interviewed using the conventional method and International Consultation on Incontinence Questionnaire (ICIQ) Female LUTS long form validated in Indonesian language in the gynecology outpatient clinic in Dr. Cipto Mangunkusumo Hospital.

Result: Using the conventional method, proposing only one question of urinary disturbance without asking the detailed symptoms, a low prevalence of LUTS was obtained (17.3%). On the other hand, with a well-structured questionnaire using ICIQ-FLUTS long form, the prevalence of LUTS was 95.3%. This result revealed that LUTS was a common condition among Indonesian women in the study population with vaginal delivery as the common risk factor.

Conclusion: Screening for LUTS using a structured questionnaire identified a significantly higher prevalence of LUTS than the conventional method. The ICIQ-FLUTS long form validated in Indonesian language is a robust questionnaire that can be recommended for use in epidemiological research as well as routine clinical practice.

[Indones J Obstet Gynecol 2015; 2: 100-105]

Keywords: ICIQ FLUTS long form, Indonesia, LUTS, prevalence, women

Abstrak

***Tujuan**: Untuk memperoleh data prevalensi gejala saluran kemih bawah pada perempuan di RS Dr. Cipto Mangunkusumo, Indonesia.*

***Metode**: Kami melakukan studi deskriptif dan analitik dengan pengumpulan data menggunakan kuesioner. Subjek penelitian ini yaitu perempuan yang datang ke poliklinik Ginekologi RS Dr. Cipto Mangunkusumo Jakarta. Subjek kami menjalani wawancara menggunakan metode konvensional dan menggunakan International Consultation on Incontinence Questionnaire (ICIQ) Female LUTS long form yang divalidasi ke Bahasa Indonesia.*

***Hasil**: Menggunakan metode konvensional yang hanya menanyakan sebuah pertanyaan tentang gangguan berkemih tanpa menanyakan gejala yang lebih detail, didapatkan prevalensi LUTS yang rendah (17,3%). Di sisi lain, dengan menggunakan kuesioner yang terstruktur menggunakan ICIQ- FLUTS long form, prevalensi LUTS adalah 95,3% pada populasi penelitian. Hal ini menunjukkan bahwa LUTS mempunyai prevalensi yang tinggi pada populasi studi dengan faktor risiko umum berupa persalinan pervaginam.*

***Kesimpulan**: Skrining LUTS dengan menggunakan kuesioner terstruktur dapat mengidentifikasi prevalensi LUTS yang lebih tinggi secara signifikan dibandingkan metode konvensional. ICIQ-FLUTS long form yang divalidasi dalam Bahasa Indonesia direkomendasikan untuk digunakan pada penelitian epidemiologi dan dalam praktek klinik sehari-hari.*

[Maj Obstet Ginekol Indones 2015; 2: 100-105]

***Kata kunci**: ICIQ FLUTS long form questionnaire, Indonesia, LUTS, perempuan, prevalensi*

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INTRODUCTION

Lower Urinary Tract Symptom (LUTS) is a condition commonly seen in women, mostly in old age.[1] Urinary incontinence as a LUTS component was considered a major problem in women and the prevalence is 17-50% in the adult population around the globe.[2] Another problem needing to be underlined is the cost to overcome these daily complaint.[2,3] LUTS is considered a subjective indicator of a disease or change in condition as perceived by the patient, care giver or partner and may lead him/her to seek help from health care professionals.[2]

The Asia-Pacific Continence Advisory Board have conducted an Asian-wide epidemiologic survey on urinary incontinence to determine the magnitude of the problem. Philippines, Singapore, Malaysia, Thailand, and Indonesia were among the participating countries. The result of urinary incontinence prevalence in Indonesia is 10.6%.[4] Junisaf

and Agustina reported the prevalence of overactive bladder among women working in the Department of Obstetrics and Gynecology in Dr. Cipto Mangunkusumo Hospital to be 15.6%.[5] Several studies concerning LUTS prevalence in Asia obtained the prevalence of LUTS to vary between 28-69%.[6] LUTS, as an extensive indicator of lower urinary tract condition in Indonesia is yet to be studied. This condition had encouraged us to do a research using conventional question method and a structured questionnaire to obtain an accurate baseline prevalence of LUTS. This will further define the magnitude of the problem of LUTS affecting Indonesian women in general.

Risk factors of LUTS such as age, parity, mode of delivery, obesity, hysterectomy, drugs affecting micturition, menopausal state, and family history of LUTS were also studied in this research, to establish the distribution in the population.[1,2,4,7-16]

In many countries, a standardized questionnaire to inquire for clinical symptoms of lower urinary tract disturbances is used in everyday practice. In Indonesia, this practice is not yet reinforced. Many clinicians depend on a simple question asking whether the patient had any urination disturbance. This is perceived as the conventional method for screening of LUTS in daily clinical practice. Questionnaire based practice is currently not a regular practice in Indonesia. Few questionnaires recommended by the International Continence Society are ICIQ-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), Urogenital Distress Inventory (UDI-6/short form), Stress Incontinence Questionnaire (SIQ), and Symptoms Severity Index (SSI).[17] ICIQ-FLUTS long form is an extensive questionnaire to assess LUTS in women, which has already been adopted in many hospitals around the world and validated in many foreign languages from its English version. This study also validates the ICIQ-FLUTS questionnaire in Indonesian language so that it can be used properly in clinical settings throughout Indonesia.

METHOD

This study is a descriptive cross sectional study. It was conducted in the gynecology outpatient clinic in Dr. Cipto Mangunkusumo National Hospital (RSCM), Indonesia from 2012-2013. RSCM is a top referral hospital in Indonesia, treating referred patients from many regions in Indonesia. With the diversity of patients, RSCM is the representative of Indonesian standard in health platform.

Our subjects were women attending the gynecology clinic in RSCM with consecutive sampling method. With the predicted prevalence of LUTS being 50%, the minimal number of subjects required was 98 women. Each subject was interviewed using standardized questionnaire comprised of the conventional method of questioning: "Do you have any complaint of urination?" and a set of Indonesian version of ICIQ-FLUTS long form. Any patient that was proven pregnant at the time of interview was excluded from the research, since pregnancy itself causes a physiological change in the micturition pattern. Information of several risk factors affecting LUTS were also obtained, including BMI calculation, age, parity, mode of delivery, obesity, history of hysterectomy, drugs affecting micturition, menopausal state, and family history of LUTS. Other data such as history of stroke or other accompanying disease were also recorded, with the consideration that this condition could also contribute to changes in voiding pattern.

The original ICIQ-FLUTS long form was provided by Dr. Nikki Cotterill from Bristol Urological Institute, England. Questionnaire validation steps were provided by ICIQ. Research subjects underwent height, body weight, and blood pressure measurements. Then a series of questions from the research questionnaire will be conducted by the researcher and trained medical students. Participants with LUTS underwent further examination in the urogynecology clinic to determine the possible etiology of LUTS.

Statistical analysis was performed using Statistical Package for The Social Sciences (SPSS) version 6, Cronbach's α was calculated to evaluate the questionnaire's internal consistency. A minimum value of 0.70 was desirable for this study.

RESULTS

The validation steps provided by the ICIQ was carried out, with the original questionnaire being translated by a sworn translator in a language institution owned by the University of Indonesia. After an Indonesian version was completed, a back-translation process by another sworn translator who was unaware of the original questionnaire was conducted to produce the back translation of

the questionnaire. These results of questionnaire were used in preliminary research in clinical setting with the targeted population. Then a validation panel consisting of urogynecology experts as well as both of the sworn translator involved in the translation process held a consensus meeting to discuss the linguistic problems encountered in the preliminary research. The discussion emphasized on linguistic and clinical perspective of each question item. Differences of words and terms used in the questionnaire were debated to decide which would be used. This step was done to maintain conceptual and technical equivalence between the source and target language. The back-translation was also compared to the original version and the differences were discussed. The results of this meeting were two sets of questionnaires, in Indonesian language and back translation were sent back to ICIQ for further validation. The Indonesian questionnaire was used in this research until the minimal number of subjects was obtained. A statistical analysis generated the Cronbach's α value of the questionnaire; the internal consistency was satisfactory with Cronbach's α of 0.78.

A total of 278 women participated in this study, with all of them completing the research questionnaire with each method, conventional and structured questionnaire. Based on the conventional method, LUTS prevalence was only 17.3%, with 48 women frankly complaining about disturbance in urination process. After that, the same subject will answer a series of question directed by the researcher in order to complete the Indonesian version of ICIQ-FLUTS long form. From this detailed, structured questionnaire we obtained a LUTS prevalence of 95.3%. Only 13 participants were negative for LUTS from all the 18 points of the questionnaire. Nocturia contributed to as much as 86.7% of all positive LUTS results, followed by stress urinary incontinence amounting to approximately 36.7%.

As much as 55% of our sample was older than 40 years old, being almost equal with the 40 years old or younger subgroup. Around 40.3% were multiparous (parity 2-4), with nulliparous subjects making up around 36.7% of the sample group. Approximately 47.5% of our samples had vaginal delivery. The BMI of the samples was generally in the normal range (40.3% had normal BMI), with obesity only making up 25.2% of our sample. Up to 78.8% of our sample were pre-menopausal women and only 5% regularly consumed medication affecting the urination process. Only 2 subjects had a history of hysterectomy, both found to have LUTS. There was no family history of LUTS in 95% of the population. Additional data concerning other diseases that could have an impact in LUTS was diabetes mellitus and stroke, where 10 women had diabetes mellitus and 7 more admitted to having hypertension. None of the participants ever had stroke. Among the participants, 16 of them regularly consumed coffee or alcohol, these two beverages known to have an effect on urination process. Women that had disability due to some extent of LUTS thus forcing them to use pads or tissue or increased frequency in changing underwear consist of 31 participants (11%). Table 2 present the distribution of LUTS according to risk factors.

Table 1. LUTS Prevalence According to Symptom Using ICIQ- FLUTS Long Form

Symptoms	n (%)
Frequency	34 (12.2%)
Nocturia	241 (86.7%)
Urgency	75 (27%)
Urge incontinence	81 (29.1%)
Bladder pain	73 (26.3%)
Stress incontinence	102 (36.7%)
Insensible incontinence	35 (12.6%)
Amount of leakage	41 (14.7%)
Hesitancy	52 (18.7%)
Straining	42 (15.1%)
Intermittent stream	49 (17.6%)
Nocturnal enuresis	31 (11.2%)
Reduced Stream	38 (13.7%)
Urinary retention	14 (5%)
Dysuria	32 (11.5%)
Incomplete emptying	81 (29.1%)
Ability to stop stream	42 (15.1%)

Questionnaire method using the comprehensive ICIQ-FLUTS long form had yielded quite a different outcome of LUTS prevalence in comparison to the conventional method. Using the questionnaire method, the proportion of subjects with LUTS negative was 4.7% versus 82.7% in the conventional method. On the contrary, the proportion of subjects with positive LUTS based on the questionnaire method was 95.3% versus 17.3% based on the conventional method.

Table 2. Population Characteristics According to Risk factors of LUTS

Variable	n (%)
Age	
< 40 years old	153 (55%)
≥ 40 years old	125 (45%)
Parity	
Nullipara	102 (36.7%)
Primipara	42 (15.1%)
Parity 2-4	112 (40.3%)
Grandemultipara	22 (7.9%)
Mode of Delivery	
Nulliparity	102 (36.7%)
Vaginal delivery	132 (47.5%)
Caesarean Section	25 (9%)
Combination	19 (6.8%)
Body Mass Index	
Underweight	29 (10.4%)
Normal	112 (40.3%)
Overweight	67 (24.1%)
Obese	70 (25.2%)
Menopausal state	
Menopause	59 (21.2%)
Pre- menopause	219 (78.8%)
Medication affecting urination	
Yes	14 (5%)
No	264 (95%)
Hysterectomy	
Yes	2 (0.7%)
No	276 (99.3%)
Family history of urination disturbance	
Yes	14 (5%)
No	264 (95%)

DISCUSSION

From this research we found that conventional method could only screen 17.3% LUTS in the population, contrast to the detailed questionnaire method that obtained LUTS prevalence of 95.3%. Only 48 participants responded to have LUTS in the initial conventional method. The remaining 230 participants declined to have any urination disturbances in the conventional method, while later most of them were positive with LUTS with one or more positive symptom based on the questionnaire method. This could occur because LUTS is possibly not the main reason they presented to the hospital in the first place, but they were instead seeking medical attention for other symptoms. Being unaware of the extensive range of symptoms in LUTS was one of the reason that most of the participants were not aware of the urination disturbances they were experiencing. Hunter et al in a similar study using a questionnaire among older women receiving home support found the prevalence of LUTS to also be high, accounting for up to 91% of all research population.[18] This prevalence was higher from that from the study by Swithinbank et al (69%)[19] and by Zhang et al in an Asian population (39.7%)[20]. This research may not entirely represent the female population in Indonesia, since there was still selection bias due to the fact that it cannot be excluded completely. Further population-based research is needed to refine the LUTS prevalence in Indonesian women. Extended range of prevalence indicates that with the right method, LUTS can be better screened in the population.

Nocturia contributed as the most common symptom indicating LUTS based on the ICIQ-FLUTS questionnaire. Nocturia is defined as the passage of urine overnight, as proposed by the Standardization Committee of The International Continence Society (ICS), with symptoms being the complaint that an individual has to wake at night one or more times to void.[2] Swithinbank et al in 1998 investigated nocturia as one element of LUTS using Bristol Female Lower Urinary Tract Symptom (BFLUTS) that was adopted as ICIQ-FLUTS long form that was also employed in this research. The result was 9% in 19-39 years old population and increasing to 51% in women ≥80 years old. In that study, the definition of nocturia was frequency of voiding at night ≥2 times.[21] This was in contrast with this research where the individual only had to wake up one time at night to void already being classified as having nocturia, and the prevalence increased up to 86.7%. Further analysis revealed that 143 participants (51.4%) had to wake up 0-1 time at night to void, this cuts down the sample that had to wake up ≥2 times at night to void to be 35.4% of all population, still higher than the previous research. Nocturia as a complaint of LUTS was studied and the result that this subjective complaint was comparable with objective data of frequency

and voiding volume of voiding diary, where 82% of all respondents accurately reported nocturia (kappa coefficient 0.70).[22]

The second most prevalent symptom was stress urinary incontinence, affecting 102 participants (36.7%). This data is surprisingly high compared to a previous study from The Asia-Pacific Continence Advisory Board conducted in Indonesia, with the prevalence of urinary incontinence to be 10.6%.[4] The different study objective, population and screening tool was probably the reason for the different prevalence rate. We were also aware that many of the participants were positive not only for one symptom, but also multiple symptoms. This will be an initial data for clinicians to utilize better screening method in the community population, considering so many women suffer from incontinence.

Age distribution in this research is mostly <40 years old. Our sample was not dominated by old women, but there is an equal distribution with the younger population. It was estimated that LUTS also happened in young age, even though many studies stated that the risk of developing LUTS increases with age.[8,9,11,12] Distribution of parity in this research is dominated by the multiparous subgroup (parity 2-4) with vaginal mode of delivery experienced by 47.5% of the samples. Based on other literature, parity is one proven risk factor for incontinence.[1,8,13,14] Nevertheless, a study by Zalina et al confirmed that nulliparous women also showed a high prevalence of LUTS, accounting for 52.7% of all the study population.[23] Also corresponding with previous studies, this research found that most women delivered their babies vaginally. This could explain the high prevalence of stress urinary incontinence among the population.

Compared to several studies documenting increasing risk of incontinence in obese women, this study documented a surprising domination of women with normal BMI (40.3%) in the population, with only 25.2% classified as obese. Obesity was not the only risk factor for LUTS, other conditions also play a role contributing in the development of LUTS.

Estrogen plays an important role in the voiding process, so it was predicted that menopausal state will increase LUTS prevalence in women.[1] This research revealed that 78.8% of our sample is in pre-menopausal state. This could indicate that LUTS also affects pre-menopausal women, especially with other contributing risk factors existing in one individual. This could also represent the possibility of higher LUTS prevalence in a wider, more balanced community consisting of an equal proportion of pre- and post-menopausal women. This will be a good focus for further studies.

Only 2 women had undergone total hysterectomy due to postpartum hemorrhage in caesarean section and due to benign uterine abnormality. Both subjects admitted having symptoms of LUTS. Systematic review by Brown et al[16] concluded that women above 60 years old with hysterectomy operation had 6 times the relative risk to develop urinary incontinence.

A small number of participants (5%) consume regular medication that may affect the urination process. ACE inhibitors, calcium channel inhibitors, and NSAIDs (in this case aspirin) were used for hypertension medication. NSAID utilization will cause water retention; ACE inhibitors will cause coughing that further exacerbates existing stress incontinence. Calcium channel inhibitors have the side effect of overflow incontinence and urinary retention. On the other side, the same amount of participants consumed coffee or alcohol, which caused alteration in urination frequency.

Mushkat et al stated that genetic transmission correlates with incidence of stress urinary incontinence in first stage relatives.[7] In our study, only 5% of all participants claimed having a relative with urination disturbance.

CONCLUSION

Method of screening plays an important role in producing an accurate rate of prevalence. Conventional method lacking information in detailed symptoms, will lead to false LUTS prevalence. Conventional method leads to a LUTS prevalence of 17.3% in the study population, while ICIQ-FLUTS long form, which inquires precise, detailed symptoms of LUTS, produced 95.3% prevalence of LUTS, significantly higher than the conventional method. This data proved that LUTS is a frequent condition among the women included in the study, with the risk factor of multiple vaginal deliveries. Unrecognized symptoms and wrong perception that LUTS is a normal condition that mostly happened in parous and old, aging women were reasons that these women didn't seek for help. This initial research

calls for further population-based research of LUTS in Indonesia. Good screening method will be the first step to recognize any pathology of the lower urinary tract in women, thus later will increase the quality of life of women with LUTS. The ICIQ-FLUTS long form questionnaire is a brief and robust questionnaire that is recommended for use in epidemiological research, as well as routine clinical practice.

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Research Article

Clinical Evaluation of Neoadjuvant Chemotherapy Followed by Radical Hysterectomy in the Management of Cervical Cancer Stage IIB

Evaluasi Klinis Kemoterapi Neoadjuvan Diikuti oleh Radikal Histerektomi dalam Pengelolaan Kanker Serviks Stadium IIB

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Abstract

Objective: To evaluate the clinical efficacy, operability, radicality, toxicity, and incidence of recurrences of neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) among patients with stage IIB cervical cancer.

Method: This is an observational clinical study at Dr. Moh. Hoesin Hospital, Palembang. Data were analyzed from 27 patients who matched the inclusion criteria and underwent 3 cycles of neoadjuvant chemotherapy (NAC) with Paclitaxel (75 mg/m^2) in combination with Cisplatin (50 mg/m^2) and Docetaxel (75 mg/m^2) combined with Carboplatin (300 mg/m2) according to AUC 6, followed by radical hysterectomy from January 2012 until December 2013.

Result: The operability rate after NAC was 96.4%. Lymph node metastases were negative in 75% of patients, and we found bilateral lymph node metastases in 14.3% of patients. Parametric infiltrations were negative in 85.7% of the patients, and positive in 14.3% of patients. No vaginal infiltrations were found. As much as 89.3% of the patients did not experience any side effect, while anemia and thrombocytopenia were found in 10.8% of the patients. We found that 7.1% of patients had recurrences within 6 months interval.

Conclusion: NAC followed by radical hysterectomy showed significant advantages for patients with stage IIB cervical cancer, with fewer side effects. However, long-term evaluation and a larger number of patients are required to confirm this result.

[Indones J Obstet Gynecol 2015; 2: 106-109]

Keywords: cervical cancer, neoadjuvant chemotherapy, radical hysterectomy

Abstrak

***Tujuan**: Untuk mengetahui efikasi klinis, operabilitas, radikalitas, toksisitas, dan angka rekurensi dari pemberian kemoterapi neoadjuvan diikuti dengan histerektomi radikal pada pasien kanker serviks stadium IIB.*

***Metode**: Penelitian ini adalah penelitian observasional klinis yang dilakukan di RSUP Dr. Moh. Hoesin, Palembang. Data dianalisis dari 27 pasien yang memenuhi kriteria inklusi, dan menjalani kemoterapi neoadjuvan dengan regimen Paclitaxel (75 mg/m^2)-Cisplatin (50 mg/m^2) dan Docetaxel (75 mg/m^2)-Carboplatin (300 mg/m^2) berdasarkan AUC 6, sebanyak 3 siklus dilanjutkan dengan histerektomi radikal dari Januari 2012 sampai Desember 2013.*

***Hasil**: Angka operabilitas setelah dilakukan kemoterapi adjuvan adalah 96,4%. Pada 75% pasien tidak ditemukan metastasis ke kelenjar getah bening, dan didapatkan metastasis ke kelenjar getah bening bilateral pada 14,3% pasien. Tidak ditemukan infiltrasi parametrium pada 85,7% pasien, dan ditemukan infiltrasi pada 14,3% pasien. Tidak ditemukan infiltrasi vagina pada seluruh pasien. Didapatkan efek samping berupa anemia dan trombositopenia sebanyak 10,8%, sedangkan pada 89,3% pasien tidak didapatkan efek samping. Sebanyak 7,1% pasien mengalami rekurensi dalam interval 6 bulan setelah pembedahan.*

***Kesimpulan**: Kemoterapi neoadjuvan diikuti dengan histerektomi radikal memberikan manfaat yang signifikan pada pasien kanker serviks stadium IIB. Namun, untuk mengkonfirmasi hasil dari penelitian ini dibutuhkan evaluasi jangka panjang dan jumlah sampel yang lebih besar.*

[Maj Obstet Ginekol Indones 2015; 2: 106-109]

***Kata kunci**: histerektomi radikal, kanker serviks, kemoterapi neoadjuvan*

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INTRODUCTION

Globally, cervical cancer is the third most common female cancer, with over 500,000 new cases diagnosed every year according to the WHO.[1] More than 85% of these cases and deaths occur in economically developing and medically underserved countries, largely in sub-Saharan Africa, South America, and South-Central Asia, where it is often the second most common female cancer. There are still almost 300,000 deaths from this disease recorded annually.[2]

According to the staging of cervical cancer by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, stage IIB is a locally advanced stage of disease, characterized by tumor larger than 4 cm, with involvement of the upper ⅔ of the va-

gina, bilateral or unilateral parametrial involvement without extension to the pelvic sidewall.[3] Currently, there is no international agreement on how FIGO stage IIB patients should be treated. The National Comprehensive Cancer Network (NCCN) guidelines recommend cisplatin-based chemoradiotherapy as a primary treatment for FIGO stage IIB disease. More recently, several opinions have been voiced on the efficacy of neoadjuvant chemotherapy (NAC) followed by surgery compared to concomitant radiotherapy and chemotherapy in patients with FIGO IIB cervical cancer.[3-5]

In this study, we aim to evaluate the clinical efficacy, toxicity, and recurrences of neoadjuvant chemotherapy followed by radical hysterectomy (RH) among patients with cervical cancer stage IIB.

METHODS

This is an observational clinical study at Dr. Moh. Hoesin Hospital, Palembang, Indonesia. Data were analyzed from 28 patients with stage IIB cervical cancer who underwent treatment between January 2012 and December 2013. Approval was provided by the Research Ethics Committee.

Patients were evaluated by board-certified gynecologic oncologists. The evaluation consists of physical examination, transvaginal ultrasonography, and thoracic radiography. Intravenous pyelography, magnetic resonance imaging, and computed tomography were performed as considered appropriate.

The inclusion criteria were all patients who underwent neoadjuvant chemotherapy for 3 cycles followed by type III radical hysterectomy, unless it was contraindicated, as determined by physical examination. The regimens of NAC were cisplatin-paclitaxel, and docetaxel-carboplatin with a three weekly interval. The exclusion criteria were patients who received more than 3 cycles of NAC, and refused to undergo radical hysterectomy.

Periodic follow-up of patients included postoperative adjuvant therapy, physical examination, vaginal cytology, and imaging such as thoracic radiography, computed tomography, or magnetic resonance imaging continued until March 2014. All data from the patients were recorded and analyzed using SPSS version 18.0.

RESULTS

During the study period, 28 patients with stage IIB cervical cancer were treated in Dr. Moh. Hoesin Palembang, Indonesia. All of them received 3 series of NAC with the regimen Docetaxel-Carboplatin and Paclitaxel-Cisplatin. The kinds of regimen the patients received are detailed in Table 1. Twenty-seven of them then underwent radical hysterectomy. As many as 26 patients (92.9%) underwent type II radical hysterectomy, and one of them (3.6%) underwent type I radical hysterectomy.

The age of the patients ranged from 29 to 59 years old. The majority of our patients had squamous cell carcinoma of the cervix (82.1%). The clinical features of our patients before NAC and the type of histopathology are summarized in Table 2.

After being treated with NAC, the patients were evaluated; and 27 of them were assessed as operable and underwent radical hysterectomy. One of them was found to be inoperable.

The toxicities associated with NAC were predominantly grade 1 and grade 2, including bone marrow suppression with leukopenia, thrombocytopenia, and a decrease in hemoglobin, which were in 3.6% of the patients for each group. No grade 3 and 4 toxicities were observed.

Metastasis was evaluated according to the pathologic data reported from surgical specimens including lymph nodes metastasis, positive surgical margin, and parametric infiltration. Positive surgical margin was found in one patient (3.6%) and 26 patients did not have infiltration in the surgical margins. Four of the patiens (14.3%) showed parametric infiltration. Four patients (14.3%) showed bilateral lymph node metastases, and 2 patients showed unilateral lymph nodes metastases. The clinical features of our patients after surgery are presented in Table 3.

Table 1. Main Regimens of NAC

Regimen	Number of Patients Based on Histopathologic Types		
	Squamous	Adenocarcinoma	Clear cell
Docetaxel - Carboplatin	2		
Paclitaxel - Cisplatin	21	4	1

Table 2. Clinical Features of the Study Subjects (n=28)

	n (%)
Age	
29-39	4 (14.3%)
40-49	14 (50%)
50-59	10 (35.7%)
Tumor diameter, cm	
≤ 4 cm	17 (60.7%)
>4 cm	11 (39.3%)
Histology	
Squamous	23 (82.1%)
Adenocarcinoma	4 (14.3%)
Clear cell	1 (3.6%)
Cancer free space (CFS)	
25%	3 (10.7%)
50%	13 (46.4%)
75%	4 (14.3%)
100%	8 (28.6%)
Operability	
Operable	27 (96.4%)
Not operable	1 (3.6%)
Type of hysterectomy	
Type II	1 (3.6%)
Type III	26 (92.9%)
Not performed	1 (3.6%)
Toxicities	
Grade I	1 (3.6%)
Grade II	1 (3.6%)
None	26 (92.8%)

Table 3. Clinical Features after Radical Hysterectomy

	n (%)
Positive lymph nodes	
Bilateral	4 (14.3%)
Unilateral	2 (7.1%)
Negative	21 (75%)
Unknown	1 (3.6%)
Parametrial invasion	
Positive	4 (14.3%)
Negative	23 (82.1%)
Unknown	1 (3.6%)
Surgical margin	
Positive	1 (3.6%)
Negative	26 (92.8%)
Unknown	1 (3.6%)

Local recurrence to the vagina after 6 months was observed in two patients, and 26 patients showed no incidence of recurrence. Until May 2014, the survival rate of the patients showed that 27 of the patients (96.4%) were still alive with no progression of disesase, while one patient (3.6%) died due to disease complication.

Table 4. Treatment Outcome

	n (%)
Local recurrence after 6 months	
Positive	2 (7.2%)
Negative	26 (92.8%)
Death	
Positive	1 (3.6%)
Negative	27 (96.4%)

DISCUSSION

Neoadjuvant chemotherapy is widely used in stage IIB cervical cancer patients. In this study all patients were given three cycles of intravenous NAC with three weekly intervals. This method is convenient and does not require any special equipment. In this study, NAC showed greater clinical values.[4,6,7]

It remains controversial as to whether NAC confers any clinical benefits in the treatment of cervical cancer. In a phase III trial in stage IB2 cervical cancer comparing NAC followed by surgery with surgery alone. Eddy et al reported similar recurrence rates and death rates between the two groups, and no evidence that NAC conferred any additional objective benefits.[7] Nevertheless, NAC continues to be used as it may contribute to ease surgical intervention by reducing tumor size. It may also be useful as a preliminary treatment while the patient is on a waiting list for surgery.[8-10] Matsumura et al showed an average of 1.4 courses of NAC with as many as 58.7% (27/46) of the patients receiving only one cycle of NAC, suggesting that the benefit conferred was that of tumor reduction rather than survival benefit.[11] Platinum-based chemotherapy was considered the most effective regimen in chemotherapy for cervical cancer. Sugiyama et al reported a 78% response rate for this combination in NAC for cervical cancer.[12]

The few studies using NAC (platinum-based) to treat cervical cancer have reported a response rate

of 66.6% to 94%. In this study, after receiving 3 cycles of NAC prior to radical hysterectomy, we found that 96.4% of patients were operable, and only one patient was not operable. Grade 1 and grade 2 toxicities were found in 3.6% of patients in both groups. Positive surgical margins were found in one patient (3.6%). Whereas, four of the patients (14.3%) showed parametric infiltration, 14,3% of patients showed bilateral lymph nodes metastases, and two of them showed unilateral lymph node metastases. Local recurrence to the vagina after 6 months was found in two patients. The survival rate of the patients showed that 27 of the patients (96.4%) were still alive with no progression of disease after 6 months, while one of the patients (3,6%) died due to disease complication.

CONCLUSION

In summary, the results of the current study indicate that NAC followed by radical hysterectomy is a viable option in the treatment of stage IIB cervical cancer. This treatment may allow avoidance of the long-term toxicities that can arise from radiotherapy and chemotherapy alone. NAC appears to offer an advantage in terms of tumor reduction prior to surgical intervention, with mild toxicity.

Further studies are needed, with a bigger sample size in a multicenter randomized clinical trial setting, and with longer duration of follow up.

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Research Article

Survival and Side Effects of Cisplatin/Cyclophosphamide and Carboplatin/Paclitaxel Adjuvant Chemotherapy in Stage IC-IV Ovarian Cancer

Kesintasan dan Efek Samping Kemoterapi Adjuvan Cisplatin/Cyclosphosphamide dan Carboplatin/Paclitaxel pada Kanker Ovarium Stadium IC-IV

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Abstract

Objective: To compare the survival and side effects in epithelial ovarian cancer patients receiving adjuvant chemotherapy of cisplatin/cyclophosphamide and carboplatin/paclitaxel.

Method: We recruited epithelial ovarian cancer patients receiving cisplatin/cyclophosphamide (group A) or carboplatin/paclitaxel (group B) adjuvant chemotherapy after surgery. Chemotherapy was given for six cycles. Overall survival and side effects were assessed.

Result: A total of 49 patients were recruited, consisting of 25 patients for group A and 24 patients for group B. In this study, the overall survival of stage IC-IV ovarian cancer patients was 37.3 months in group A (95%CI=31.86-43.46) and 35.5 months (95%CI= 13.93-43.46) in group B (p<0.001). Hematologic side effects of both groups were not significantly different, i.e: leukopenia 12% vs 18% (p=0.14) and thrombocytopenia 5.3% vs 9.7% (p=0.38) in group A and group B, respectively. Gastrointestinal toxicity occurred more frequently in group A, i.e: nausea 38.6% vs 22.9% (p<0.05), vomitus 24.6% vs 11.8% (p<0.05) in group A and group B, respectively. Symptoms of peripheral sensory neuropathy were found in 5.33% of group A subjects and 23.6% of group B (p<0.05).

Conclusion: Overall survival in this study is better in patients receiving cisplatin/cyclophosphamide than patients receiving carboplatin/paclitaxel. However, further study with larger sample is still needed. The gastrointestinal side effects are found more frequently in the cisplatin/cyclophosphamide group, while peripheral sensory neuropathy and hematologic side effects are more frequent in the carboplatin/paclitaxel group.

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Keywords: carboplatin/paclitaxel, cisplatin/cyclophosphamide, ovarian cancer, overall survival, side effects

Abstrak

***Tujuan**: Membandingkan kesintasan dan efek samping antara pasien kanker ovarium tipe epitelial yang menerima kombinasi kemoterapi cisplatin/cyclosphosphamide dengan carboplatin/paclitaxel.*

***Metode**: Pasien kanker ovarium epitelial mendapat ajuvan kemoterapi dibagi menjadi dua kelompok berdasarkan jenis obat yang diterima; kelompok A yaitu kelompok yang menerima cisplatin/cyclophosphamide, dan kelompok B yaitu kelompok yang menerima carboplatin/paclitaxel. Kemoterapi diberikan sebanyak enam siklus. Dilakukan penilaian kesintasan dan efek samping masing-masing kelompok.*

***Hasil**: Terdapat 49 pasien dalam penelitian ini, terdiri dari 25 pasien dalam kelompok A dan 24 pasien dalam kelompok B. Kesintasan keseluruhan kanker ovarium stadium IC-IV pada kelompok A yakni 37,3 (IK95%=31,86-43,46) bulan, sedangkan kelompok B yakni 35,5 (IK95%=13,93-43,46) bulan (p<0,001). Efek samping hematologi tidak berbeda secara signifikan, di mana pada kelompok A didapatkan leukopenia sebanyak 18% dan trombositopenia 9,7%, sedangkan pada kelompok B sebanyak 12% dan 5,3% (p=0,14 dan 0,38). Toksisitas gastrointestinal lebih sering terjadi pada kelompok A, di mana didapatkan keluhan mual sebanyak 38,6% dan muntah sebanyak 5,33%, sedangkan pada kelompok B sebanyak 22,9% dan 11,8% (p<0,05). Gejala neuropati perifer lebih sering pada kelompok B, yakni sebanyak 23,6% dibandingkan pada kelompok A, yakni 5,33% (p<0,05).*

***Kesimpulan**: Kesintasan keseluruhan secara signifikan lebih baik pada kelompok cisplatin/cyclophosphamide dibandingkan kelompok carboplatin/paclitaxel. Namun, diperlukan studi lebih lanjut dengan sampel yang lebih besar. Efek samping sistem gastrointestinal lebih sering terjadi pada kelompok cisplatin/cyclophosphamide, sedangkan sistem hematologi dan saraf lebih sering terjadi pada kelompok carboplatin/paclitaxel.*

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***Kata kunci**: carboplatin/paclitaxel, cisplatin/cyclosphosphamide, efek samping, kanker ovarium, kesintasan keseluruhan*

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INTRODUCTION

Ovarian cancer is the seventh most common female cancer worldwide in 2012.[1] Each year, 22,280 new cases are diagnosed, leading to 15,500 deaths.[2] This cancer is the leading cause of death among gynecological cancers. There is usually no

symptom in the early stages, and most of the time symptoms present in an advanced stage. More than 75% of patients present with advanced stage or stage III-IV according to the International Federation of Gynecology and Obstetrics (FIGO) classification.[3-6] In Indonesia, according to the Indonesian Society of Gynecologic Oncology (INASGO), the incidence of ovarian cancer was 363 cases in 2013.[7]

More than three decades ago, the standard adjuvant chemotherapy treatment of ovarian cancer in the United States was cisplatin/cyclosphosphamide (CC). McGuire et al, held a randomized study in the Gynecologic Oncology Group (GOG) 111 comparing the use of CC and carboplatin/paclitaxel (CP). The progression-free survival was significantly longer ($p<0.001$) in the CP group compared to the CC group (median 18 vs 13 months). Overall survival was also longer ($p<0.001$) in the CP group than in the CC group (median 38 vs 24 months).[8]

Chemotherapy has numerous known side effects, including bone marrow suppression, liver disorders, GI tract disorders, renal toxicity, neurotoxicity and ototoxicity. Cisplatin generally has more side effects compared to carboplatin, except in terms of hematologic effects, especially granulocytopenia and thrombocytopenia. Currently, carboplatin and paclitaxel is used as the standard adjuvant chemotherapy that shows good effectivity and less side effects, although they are quite expensive compared to the older regimen of cisplatin and cyclophosphamide.

Therapy for epithelial ovarian cancer according to INASGO guidelines, consists of administration of 50-100 mg/m^2 cisplatin or AUC 5-6 carboplatin, combined with 600 mg/m^2 cyclosphosphamide or 175 mg/m^2 paclitaxel.[9]

In Indonesia there is no data on the survival and side effects of different regimens of chemotherapy in patients with advanced ovarian cancer. The aim of this study is to compare the overall survival and side effects of cisplatin/cyclophosphamide and carboplatin/paclitaxel chemotherapy regimens.

METHODS

This historical cohort study's target population were patients with stage IC-IV epithelial ovarian cancer who presented to Dr. Cipto Mangunkusumo Hospital gynecologic oncology clinic, from January 1st 2008 to December 1st 2013.

We included all patients with stage IC-IV ovarian cancer patients who have undergone surgery and received adjuvant chemotherapy of cisplatin and cyclophosphamide or carboplatin and paclitaxel, had a performance status score ≤ 2 based on the Eastern Cooperative Oncology Group (ECOG) criteria, and whose laboratory results were within normal limits. Patients were excluded if they received fewer than 6 cycles of chemotherapy, or had abnormal laboratory results prior to chemotherapy.

Patients who met the criteria were examined clinically and using ultrasound (Accuvix® XQ, Medison, Seoul, Korea). Some were also selectively examined using CT Scan and MRI before undergoing debulking laparotomy or surgical staging. Chemotherapy were given intravenously for at least 6 cycles. The dose of cisplatin was 50 mg/m^2 in combination with 600 mg/m^2 cyclophosphamide. Carboplatin dose was 300 mg/m^2 or AUC 6, combined with 175 mg/m^2 paclitaxel. Progression-free and overall survival were assessed after 6 cycles of chemotherapy by referring to patients' medical records, direct interviews, and phone call interviews. Adverse effects were assessed after each cycle using the National Cancer Institute (NCI) Common Toxicity Criteria version 1. The data were statistically analyzed using Stata version 12 program (Stata Corp. LP, Texas, USA).

RESULTS

The number of epithelial ovarian cancer patients who met the inclusion and exclusion criteria was 70 patients. The subjects were then divided into 2 groups, group A comprised of 35 (43.21%) cases treated with cisplatin/cyclosphosphamide, and group B comprised of 46 (56.79%) cases treated with carboplatin/paclitaxel chemotherapy regimen. At the end of the study, 21 patients were dropped out of the study, because they did not finish six cycles of chemotherapy. Therefore, 25 patients (71.43%) in group A and 24 patients (53.17%) in group B were accounted for analysis,

The patients recruited in this study have a tendency for equally distributed characteristics between the two groups. The costs per cycle of chemotherapy in both groups were expectedly different. The cost of one cycle in group A was a lot cheaper compared to the cost in group B.

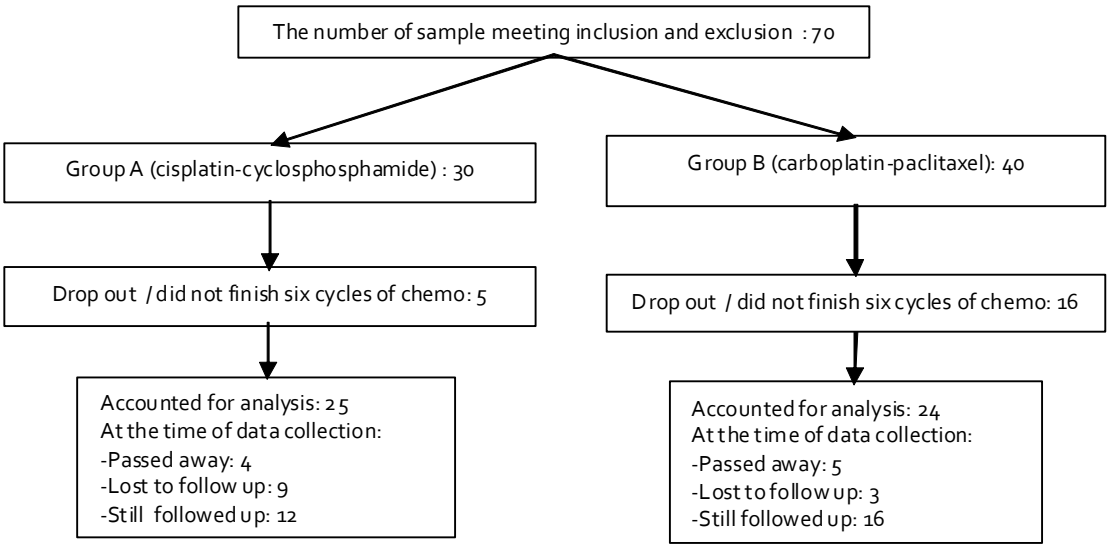

Figure 1. Sample Group Based on Chemotherapy Regimen and the Last Condition of the Patient.

Kaplan-Meier curve in Figure 2 shows both groups' survival curves. There was a significant difference between the two groups' overall survival. Overall survival of stage IC-IV ovarian cancer patients was 37.3 months in group A (95%CI=31.86-43.46) and 35.5 months (95%CI=13.93-43.46) in group B ($p<0.001$), as portrayed in Table 2.

Assessment of side effects was done based on the examination table from the NCI Common Toxicity Criteria Version 1. Assessment after each cycle is presented in Table 3.

Assessment of hematologic side effects includes hemoglobin, leukocyte, and thrombocyte counts. There were no significant differences in hematologic parameters between both groups. Statistically significant differences were found in gastrointestinal side effects. Patients in group A experienced significantly more nausea and vomiting in comparison to those in group B. However, there was no significant difference in terms of diarrhea and stomatitis between both groups. In the assessment of CNS side effects, group A reported significantly more headache than group B, but group B reported more peripheral neuropathy.

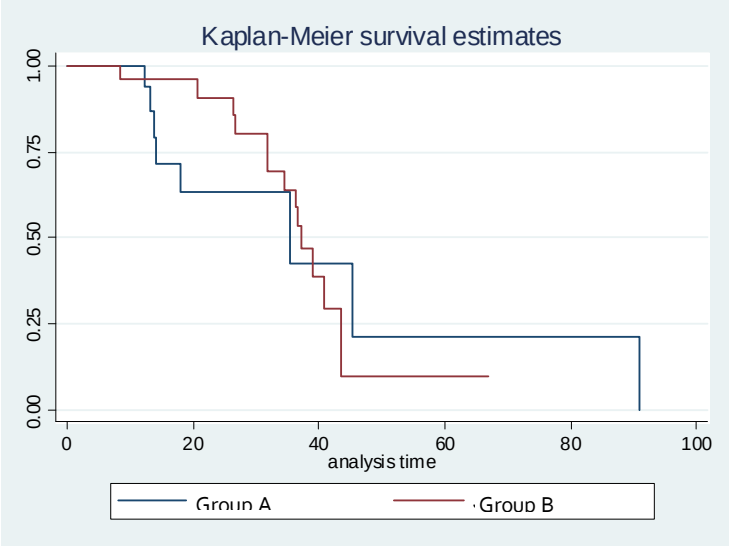

Figure 2. Overall survival of group A (cisplatin/cyclosphosphamide) and group B (carboplatin/paclitaxel).

Table 1. General Characteristics of Patients According to the Chemotherapy Treatment.

Characteristics	Group A n(%)	Group B n(%)	p-value
Age in years (med, min-max)	44 (30-61)	52.5 (44-78)	0.0003*
Parity			
0	7 (28)	6 (25)	
1	6 (24)	5 (20.83)	0.911
≥2	12 (48)	13 (54.17)	
Chief complaint			
No complaints	1 (4)	0 (0)	
Abdominal lump	21 (84)	18 (75)	0.781
Abdominal pain	1 (4)	5 (20.83)	
Dyspnea	2 (8)	1 (4.17)	
Performance status			
0	15 (60)	20 (83.3)	
1	4 (16)	2 (8.3)	0.186
2	6 (24)	2 (8.3)	
Histopathology			
Serous	10 (41.7)	10 (41.7)	
Musinosus	4 (16)	1 (4,2)	0.484
Clear cell	7 (28)	10 (41.7)	
Endometrioid	4 (16)	3 (12.5)	
Tumor grade			
Well-differentiated	13 (28.26)	7 (23.33)	
Moderate	18 (39.13)	11 (36.67)	0.490
Undifferentiated	15 (32.61)	12 (40)	
Stage			
IC	1 (4)	4 (16.7)	
II	3 (12)	4 (16.7)	0.458
III	17 (68)	13 (54.7)	
IV	4 (16)	3 (12.5)	
Stage			
Early	4 (16)	8 (33.3)	0.686
Advanced	21 (84)	16 (66.7)	
Time of administration			
Neoadjuvant	5 (20)	4 (16.7)	0.763
Adjuvant	20 (80)	20 (83.3)	
Cost per cycle (IDR)	838.787	5.532.137	<0.001*

* *p-value<0.05*

Table 2. Median of Overall Survival in Both Groups.

	Group A Cisplatin- Cyclosphosphamide	Group B Carboplatin-Paclitaxel	p-value
Median of Overall Survival (month)	37.3	35.5	<0.001
95%CI	31.86 -43.46	13.93-43.46	

DISCUSSION

A study conducted by McGuire et al[8] found significantly higher survival rate in ovarian cancer patients receiving CP chemotherapy than those receiving CC; 38 months (95%CI=32-44) vs 24 months (95%CI= 21-30). Piccart et al[10] also found that patients receiving CP had better survival compared to those receiving CC, where the survival was 35.6 and 25.8 months, respectively. Meanwhile, our results were contradictory to results of these previous studies, where our patients who received CC had a significantly longer overall survival. It suggests that in our sample, a combination of platinum-based therapy with cyclophosphamide is better than with taxanes.

However, it is too early to conclude that cyclophosphamide is better than taxanes in combination with platinum-based chemotherapy for survival. Our results could be by the lack of homogeneity in our patients. The patients in group B was relatively older than group A. The study counducted by Ries et al[11] discovered that the older the age of ovarian cancer patients, the worse the prognosis or survival. Moreover, the number of patients recruited in this study was too small, with about a third of the patients having to be excluded.

McGuire et al[8] observed that the 1st, 2nd, 3rd, and 4th degree reduction of leukocytes/neutrophil appeared in 4%, 9%, 22%, and 61% of patients in the CC group, while in the CP group they appeared in 2%, 4%, 14%, and 78% of patients, respectively. Although neutropenia of grade 3 or 4 developed in the majority of women in the CP group, the incidence of febrile neutropenia was low and was consistent with the brevity of paclitaxel-induced myelosuppression. As for gastrointestinal symptoms, the occurrence of toxicity according to severity (1st-4th degree) was 8%, 42%, 8%, and 3% in the group receiving cyclophosphamide, and 14%, 42%, 12%, and 3% in those receiving taxanes.

Piccart et al[10] found in his research that 31% of subjects in the CC group developed 3rd grade neutropenia and 40% of them developed 4th grade neutropenia. In the CP group, 3rd and 4th grade neutropenia were experienced by 32% of subjects each. Severe nausea was more often experienced by those in the CC group. Meanwhile, neurosensory symptoms appeared more frequently in CP group.

In our study, neutropenia was found in 12% of patients in group A and 18% of patients in group B. Nausea was more commonly encountered in group A in comparison to group B. Vomiting was found up to three times more frequently in group A than in group B. Furthermore, we found the prevalence of neurosensory disturbance to be 5.3% in group A, and 23.6% in group B ($p<0.05$). These results show that compared to CC combination, CP combination causes less gastrointestinal side effects but more hematologic and neurologic side effects. No apparent allergic reaction was observed in both group A and group B.

CONCLUSION

Overall survival of ovarian cancer patients in this study is better in patients receiving cisplatin-cyclophosphamide than those receiving carboplatin-paclitaxel. However, further research with a larger sample is still needed. Gastrointestinal side effects are more frequent in patients getting cisplatin-cyclophosphamide, while peripheral sensory neuropathy and hematologic side effects are found more frequently in patients getting carboplatin-paclitaxel chemotherapy.

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Research Article

A Real-time Optoelectronic Device in Screening of Precancerous Cervical Lesion

Deteksi Dini Lesi Prakanker dengan Perangkat Optoelektronik Real-Time

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Abstract

Objective: To obtain the diagnostic values of optoelectronic device for screening of precancerous cervical lesions.

Method: We performed a diagnostic study with cross sectional design. Subjects were recruited from Dr. Cipto Mangunkusumo Hospital, from February until December 2013. Subjects were enrolled based on consecutive sampling until the minimum sample was achieved (60 samples).

Result: During the study period, 60 patients were enrolled. Sensitivity, specificity, positive predictive value, and negative predictive value of the optoelectronic device were 76%, 95%, 96%, and 64%, respectively. We also investigated diagnostic values of other screening methods, namely citology and colposcopy. Sensitivity and specificity of liquid based cytology were 83% and 63% respectively. The combination of optoelectronic device and liquid based cytology increased the sensitivity to 92.8%. Meanwhile, sensitivity and specificity of colposcopy were 88% and 58%, respectively. Based on Altman criteria, kappa value for optoelectronic device with cytology was 0.35 (fair) and optoelectronic device with colposcopy was 0.45 (moderate).

Conclusion: A real-time optoelectronic device might be used as an alternative method in early detection of precancerous cervical lesions, either as a single method or combined with liquid based cytology.

[Indones J Obstet Gynecol 2015; 2: 117-120]

Keywords: diagnostic values, optoelectronic device, precancerous cervical lesions

Abstrak

***Tujuan**: Untuk mengetahui nilai diagnostik perangkat optoelektronik dalam mendeteksi lesi prakanker serviks.*

***Metode**: Studi ini merupakan studi diagnostik dengan desain potong lintang. Subjek penelitian direkrut dari Rumah Sakit Dr. Cipto Mangunkusumo, Jakarta, Indonesia dari bulan Februari hingga Desember 2013. Sampel dikumpulkan dengan metode pengambilan sampel secara konsekutif hingga jumlah minimum sampel tercapai (60 sampel).*

***Hasil**: Selama periode penelitian, didapatkan 60 pasien yang ikut serta dalam penelitian ini. Sensitivitas, spesifisitas, nilai prediktif positif, dan nilai prediktif negatif dari perangkat optoelektronik yaitu 76%, 95%, 96%, dan 64% berturut-turut. Sensitivitas dan spesifisitas sitologi berbasis cairan yaitu 83% dan 63% secara berturut-turut, kombinasi dengan perangkat optoelektronik meningkatkan sensitivitas menjadi 92,68%. Sedangkan sensitivitas dan spesifisitas kolposkopi yaitu 88% dan 58% secara berturut-turut. Nilai kappa berdasarkan kriteria Altman perangkat optoelektronik dengan sitologi yaitu 0,35 (cukup) dan dengan kolposkopi yaitu 0,45 (sedang).*

***Kesimpulan**: Perangkat optoelektronik yang hasilnya didapatkan saat itu juga dapat menjadi metode alternatif dalam deteksi dini lesi prakanker serviks, baik sebagai metode tunggal maupun kombinasi dengan sitologi berbasis cairan.*

[Maj Obstet Ginekol Indones 2015; 2: 117-120]

***Kata kunci**: lesi prakanker serviks, nilai diagnostik, perangkat optoelektronik*

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INTRODUCTION

Based on Globocan data in 2012, cervical cancer is the fourth most common malignancy worldwide after breast, colorectal, and gastric cancer, with an estimated 528,000 new cases, and almost one-third found in South - East Asian countries. Approximately 266,000 deaths from cervical cancer (7.5% of all female cancer mortality), and about 87% of cervical cancer mortality occur in developing countries.[1]

Around 20,928 new cases of cervical cancer are diagnosed each year in Indonesia, with an age-standardized incidence of 17.3/100,000 women per year.[2] Aziz et al stated that cervical cancer accounts for 75% of all gynecological cancer in an Indonesian academic hospital, with the majority presenting in advanced stages.[3] Based on registry data of Indonesian Society of Gynecology Oncology (2013), there were 446 new cervical cancer cases in Dr. Cipto Mangunkusumo Hospital, Jakarta, Indo-

nesia in 2013, and 76.68% of them presented to the health service in advanced stages.[4]

In the early stages, cervical cancer has no specific or typical signs and symptoms. Therefore, every woman is advised to undergo screening for cervical cancer as early as possible, using the method of Papanicolaou (Pap) test cytologic examination.[5] Even though the effectivity of Pap test as a screening test has not been proven with a randomized test, it has been well known to effectively decrease the incidence and mortality rate of cervical cancer in developed countries. In the United States, Pap test succeeded to change cervical cancer from the leading cause of female death to an infrequent disease, decreasing the incidence by about 75% since Pap test was found 40 years ago. However, only few countries possess adequate infrastructure and human resources to perform cervical cancer screening program, leading to the high number of cervical cancer cases in some countries, especially in developing countries.[6] In Indonesia, there are more than 13,000 islands but fewer than 300 pathologists are available, with most of them centered in urban areas. Therefore a screening method is needed, which might be as effective as Pap test or liquid based cytology (LBC) but does not require evaluation of specimens.

Recently, biophysics has emerged as a new method in the diagnosis and prevention of cervical cancer. Due to its low false positive and false negative results, biophysics method is a promising screening method for cervical cancer. Truscreen is a novel optoelectronic device utilizing this method as a screening tool for the detection of precancerous cervical lesions. This real time device uses low-level electrical and optical signals to scan the cervix. The response will be measured by computer-based expert system software, which will classify the tissue response by comparing the signals with those stored in a computer database representative of the range of cervical tissue types.[7] Because this method is automated, it might be considered for use in developing countries where the pathologists are few and are not widespread throughout the area, and can even be used by nurses or midwives.[8]

There have been no studies on the use of optoelectronic device in detecting precancerous cervical lesions in Indonesia. As it seems promising and does not heavily rely on the operator or pathologists, we tried to investigate its diagnostic values in detecting precancerous cervical lesions.

METHODS

We performed a diagnostic study utilizing cross sectional design. The subjects were recruited from Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia during the period of February until December 2013. Cervical cancer screening methods were performed in all subjects in the form of optoelectronic device (TruScreen, Polartechnics Limited, Sydney, Australia), liquid based cytology, and colposcopy followed by targeted biopsy. Human Papilloma Virus (HPV) DNA test was performed only on several subjects due to its high cost.

The patient presenting to the outpatient clinic of Dr. Cipto Mangunkusumo National Hospital in the period above, who desired to undergo cervical cancer screening or referred from other centers (midwives, public health care, OBGYN, general practitioner) with suspected precancerous cervical lesion were included in this study. Patients refusing to join this study, those with suspected or confirmed cervical cancer, and confirmed invasive carcinoma on biopsy were excluded.

The samples were enrolled based on consecutive sampling method until the minimum number of samples were achieved (60 samples). All patients gave their consent after being informed by the investigators.

Data were analyzed using SPSS 21.0. Abnormal results of optoelectronic device, biopsy, cytologic examination, colposcopy and HPV DNA examination will be showed descriptively. We analyzed diagnostic values for optoelectronic device, LBC, and colposcopy compared to the gold standard, anatomic pathology biopsy. To understand the similarity and comparison between two methods of cervical precancerous lesion screening, we determine the kappa value between optoelectronic device with LBC and colposcopy.

RESULTS

During the research period, 66 patients were recruited, and 6 patients were excluded due to invasive carcinoma result based on their biopsy. Subject characteristics are shown below.

Table 1. Subject Characteristics.

Characteristic		Data (n=60)
Age	(mean ± SD)	42 ± 9.18
History of Contraception Use	No history	10 (16.7%)
	IUD	18 (30%)
	DMPA	15 (35%)
	Oral contraceptives	8 (13.3%)
	Sterilization	9 (15%)
Level of Education	No formal education	1 (1.7%)
	Primary school	10 (16.7%)
	Middle school	27 (45%)
	High school	22 (36.7%)
Parity	Nulliparity	4 (6.7%)
	Multiparity	256 (93.3%)

There were 32 patients (53%) with abnormalities based on the optoelectronic device, 41 patients (68,3%) with precancerous cervical lesion on biopsy, 44 patients (73,3%) with abnormal colposcopy result, and 41 patients (63,3%) with abnormal LBC result. From 41 patients who had confirmed cervical precancerous lesion on biopsy, 18 (44%) had low grade squamous intraepithelial lesion (CIN 1) and 23 (56%) had high grade squamous intraepithelial lesion (CIN 2 and 3, carcinoma in situ).

Sensitivity, specificity, positive predictive value, and negative predictive value of optoelectronic device were 76%, 95%, 96%, and 64%, respectively. We also investigated the diagnostic values of other screening methods, namely cytology and colposcopy. Sensitivity and specificity of LBC were 83% and 63%, respectively. Sensitivity and specificity of colposcopy were 88% and 58%, respectively. The combination of optoelectronic device and LBC increased the sensitivity to 92,8%.

To evaluate inter-rater agreement, we analyzed the Kappa value. Kappa value for optoelectronic device with cytology was 0.35 (fair) and for optoelectronic device with colposcopy was 0.45 (moderate). These values mean optoelectronic device is quite similar or might be comparable with cytology and colposcopy in screening of precancerous cervical lesion.

DISCUSSION

In this study, we excluded cases with confirmed cervical cancer as proven by biopsy or clinical examination, because the objective of our study is to investigate the diagnostic values of optoelectronic device in detecting cervical pre-cancerous lesion as early as possible so that the patient might be treated properly before the development of cervical cancer.

In our study, the number of abnormal optoelectronic device test results was quite high (> 50%), indicating the presence of precancerous cervical lesion, either low grade squamous intraepithelial lesion (LGSIL) or high grade squamous intraepithelial lesion (HGSIL). The sensitivity of optoelectronic device in detecting precancerous cervical lesion in our study was 76%, which was in line with the study by Lee et al.[9] They concluded that Truscreen has a sensitivity of 75.8% in detecting CIN 1 and 77.3% for CIN 2/3, with 85.1% specificity. In a multicenter study of 651 subjects by Singer et al, the sensitivity of Truscreen was reported to be 67% for CIN 1 and 70% for CIN 2/3.[7] However, Allameh and Long reported lower sensitivity; 46.9% and 67.4%, respectively.[8,10]

We observed that the sensitivity of this device in detecting LGSIL (88.24%) was higher than HGSIL (96%), in contrast to the previous study, which was 67% versus 70%.[7] Different sampling methods in both studies might be the cause of this difference. Surprisingly, we observed a high specificity for optoelectronic device, which was even higher than LBC and colposcopy. This result was supported by previous studies conducted by Lee and Lim, who reported a specificity of 85.1% and 81.4, respectively.[9,11]

Pruski et al reported the area under the ROC curve of optoelectronic device to detect HGSIL and squamous cell carcinoma was 0.88, which indicates a high diagnostic value.[12]

We attempted to evaluate whether optoelectronic device was equal or more reliable in comparison to other commonly known methods of cervical cancer screening such as LBC and colposcopy. Based on inter-rater agreement analysis, kappa value for optoelectronic device with cytology was 0.35 (fair) and optoelectronic device with colposcopy was 0.45 (moderate). Therefore, we can conclude that optoelectronic device was comparable with LBC and colposcopy in detecting precancerous cervical lesion.

There are some advantages in performing optoelectronic device to detect precancerous cervical lesion, specifically in Indonesia. Automated processed result of this device will decrease the risk of human error and not having to rely on laboratory examinations, immediate results (real time examination) will reduce the number of patient visits, shortened screening-treatment timeline, reduced loss of follow-up, and finally, decreased cost in cervical cancer screening programs.

CONCLUSION

A real-time optoelectronic device might be used as an alternative method in early detection of precancerous cervical lesions, either as a single method or combined with liquid based cytology.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Research Article

CC-Human Menopausal Gonadotropin Combined with Growth Hormone in Mini-stimulation Protocol could Improve Clinical Outcome in Poor Ovarian Responders

Peran CC-Human Menopausal Gonadotropin dan Growth Hormone Meningkatkan Keberhasilan Kehamilan dengan Protokol Mini-stimulasi pada Pasien dengan Respons Ovarium yang Rendah

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Abstract

Objective: To investigate the role of CC-highly purified Human Menopausal Gonadotropin (hpHMG) and Growth Hormone (GH) in mini-stimulation protocol to improve outcome in poor ovarian responders (POR).

Method: All patients were given clomiphene citrate 150 mg from day 3 to day 7 of menstrual cycle followed by 150 IU hpHMG daily from day 8 until ovulation trigger. Two groups were observed where one group received GH and the other arm did not. In the GH group, 8 IU of GH were given from day 1 of stimulation until stimulation was stopped. GnRH antagonist was used to suppress ovulation.

Result: Among 51 eligible women, 29 patients with GH and 22 patients without GH, no difference was observed in the number of oocytes retrieved (2.21 versus 2.64) and the number of embryos transferred (1.24 versus 1.68) in the GH group versus the group without GH, respectively. Total clinical pregnancy rate was 17.6%. No significant difference in pregnancy and ongoing pregnancy rate in both groups (17.2% versus 18.2%) and (13.8% versus 13.6%), respectively. In patients older than 40 years old, GH showed a 4-fold likelihood in producing top quality embryos (44.8% vs 13.6%, OR=3.6, p=0.05).

Conclusion: CC-HMG regimen in mini-stimulation protocol is an effective option in poor responders. Additional GH in mini-stimulation program provided a higher number of top quality embryos in women older than 40 years old, although there were no difference in clinical or ongoing pregnancy rate.

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Keywords: CC-HMG, growth hormone, IVF, mini-stimulation protocol, poor ovarian responders

Abstrak

Tujuan: *Untuk menyelidiki peran CC-highly purified Human Menopausal Gonadotropin (hpHMG) dan Growth Hormone (GH) dalam protokol mini-stimulasi pada pasien dengan respons ovarium rendah yang menjalani teknologi reproduksi berbantu (IVF).*

Metode: *Semua pasien diberi 150 mg clomiphene citrate mulai hari ke 3 sampai hari ke-7 siklus menstruasi. Kemudian diikuti dengan pemberian 150 IU hpHMG setiap hari, dimulai pada hari ke-8 hingga hari dilakukannya trigger ovulasi. Subjek yang diamati dibagi menjadi dua kelompok. Kelompok pertama terdiri dari pasien dengan poor ovarian response (POR) yang diberikan growth hormone dan kelompok kedua terdiri dari pasien dengan poor ovarian response yang tidak diberikan growth hormone. Dalam kelompok GH, diberikan 8 IU GH dari hari pertama stimulasi rangsangan sampai rangsangan dihentikan. Pada kedua kelompok, GnRH antagonis digunakan untuk menekan ovulasi. Dalam penelitian ini dinilai tingkat kehamilan dan kualitas embrio per pasien.*

Hasil: *Dari 51 subjek yang memenuhi syarat, 29 pasien termasuk kelompok GH dan 22 pasien termasuk kelompok tanpa GH. Pada kelompok GH dan tanpa GH tidak ditemukan adanya perbedaan pada jumlah oosit (2,21 vs 2,64) dan jumlah embrio yang ditransfer (1,24 vs 1,68). Jumlah angka kehamilan yang dicapai adalah 17,6%. Tidak terdapat perbedaan angka kehamilan yang signifikan pada kedua kelompok (17,2% vs 18,2%) dan (13,8% vs 13,6%). Pada kelompok pasien GH berusia ≥ 40 tahun didapati kemungkinan 4 kali lipat lebih besar dalam memproduksi embrio berkualitas baik jika dibandingkan dengan kelompok usia yang sama tanpa GH (44,8% vs 13,6%; OR=3,6; p=0,05).*

Kesimpulan: *Pemberian CC-HMG dalam protokol ministimulasi merupakan pilihan yang efektif pada pasien POR. Suplementasi GH pada program ministimulasi dapat memberikan jumlah embrio berkualitas baik yang lebih tinggi pada perempuan berusia lebih tua dari 40 tahun, meskipun tidak terbukti adanya perbedaan yang bermakna pada angka kehamilan.*

[Maj Obstet Ginekol Indones 2015; 3: 140-145]

Kata kunci: *CC-HMG, growth hormone, IVF, poor ovarian responders, protokol mini-stimulasi*

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INTRODUCTION

Infertility is a common condition, affecting 10 to 15 percent of couples of childbearing age. However, nearly half of women who experience infertility will become pregnant in the second year of trying to conceive, without receiving any treatment. Most of these couples are more accurately described as subfertile, than infertile. But there are some obvious exceptions, such as women with bilateral fallopian tube obstruction or men with azoospermia.[1] In general, 25% of infertility cases can be caused by problems in men. The other 75% are caused by problems in women, with 27% cases caused by ovulatory disorders, 22% by fallopian tube and uterine disorders, 17% idiopathic and 9% by others problems. It is generally agreed that the evaluation of infertility should be considered in any couple who failed to conceive within one year.[1]

Pregnancy requires a complex series of events that include ovulation, ovum retrieval by the fallopian tube, fertilization, transportation of fertilized ovum to the uterus, and implantation to the uterine cavity.[1] Ovarian stimulation is the base of infertility treatment because it can increase the chances of conception by causing the development of multiple follicles and mature oocytes. Although rapid improvements have been made on assisted reproductive technology (ART), some patients did not experience any improvement. This is because these patients are no longer responding to the treatment given. These patients can be classified into the poor ovarian responders (POR) group. Only 9-24% women from this group can receive ovarian stimulation therapy due to the lack of response to the treatment.[2]

There are various criteria used to describe POR. The first experiment to accurately determine a woman with POR was conducted in 2011 involving the European Society for Human Reproduction and Embryology (ESHRE). The consensus has determined the minimum criteria necessary to define POR called Bologna criteria. At least two of three conditions must be met. First is being ≥ 40 years old or having any risk factors for POR (genetic or other conditions that may be linked to a decrease in the number of resting follicles). Second, having a history of previous POR (≤ 3 oocytes after conventional stimulation of at least 150 IU of FSH per day), and third was the presence of abnormalities in ovarian reserve test/ORT (eg. antral Follicle Count of 5-7 follicles or anti-Müllerian Hormone of 0.5-1.1 ng/ml).[2] From the definition, POR refers to the response of the ovaries, therefore a patient can be classified as poor responders if two episodes of POR are found after maximal stimulation has been performed, even if this patient does not meet 2 of the 3 criteria above.[3]

Recently, a lot of studies have focused in finding signs that can identify sensitive and specific criteria, which can determine whether a person has a good or poor response. Hopefully this effort will open up various avenues for counseling and selection for patients who will do IVF.[4] A number of stimulation protocols have been used to deal with the poor responders. However, the pregnancy rates as the result indicator of in vitro fertilization (IVF) still showed unsatisfactory results. Now, some studies have supported additional GH and faster embryo transfer (day two) in the IVF treatment, which is expected to increase the chances of pregnancy in poor responders.[5]

GH is produced by the pituitary gland and the ovaries. It binds to receptors in granulose, theca and luteal cells, and trigger steroid oogenesis and gametogenesis. It works directly by inducing the production of gonadotropins and indirectly by increasing regulation of LH receptors and inducing luteinization. A direct correlation between the concentration of GH in the follicle and level of oocyte maturation has recently been reported. Oocytes from follicles that have normal GH concentration are more fertile than the oocytes from follicles with a low concentration of GH. GH improves the quality of oocytes to accelerate and coordinate the cytoplasmic and nuclear maturation.[6,7]

GH supplementation has been a part of adjunctive therapy given to the protocol of controlled ovarian stimulation (COS) in the case of POR for a long time.[5] Cochrane data showed a positive effect of GH on poor responders with an odds ratio of 4.37 (95% CI 1.06-18.01).[8,9] An RCT that has not been published involving 39 patients, concluded that the addition of GH during stimulation in patients with poor response can improve pregnancy rates by 50% at a dose of 4 IU/day, 55% at a dose of 8 IU/day and 18% on placebo. GH dosing here are based on previous studies.

Currently, there are few studies evaluating GH therapy in POR patients. The problem faced is the definition of POR, which still varies in some studies due to lack of standardized POR diagnostic criteria. Although the Bologna criteria has been defined, this

criteria has been considered to fail in determining the quantity and quality of the material from oocytes, which is shown on ART outcomes, as reflected by the pregnancy rate and live births.[5]

Our study tried to observe the clinical outcome in poor ovarian responders receiving CC-HMG combined with GH through Mini-stimulation protocol. Throughout this study patients characteristics and the outcome of IVF programs such as the number of oocyte count, embryo quality, embryo count (both transferred and frozen), as well as the pregnancy rate were assessed. The objective of this study is to compare the pregnancy rate and the embryo quality per patient.

METHODS

This study is a retrospective cohort non-randomized study that was carried out in the Morula IVF laboratory in Jakarta from January 2012 until June 2013. The study was approved by the ethics committee of the Faculty of Medicine, Atma Jaya University, Jakarta; and all subjects consented to participate in the study. The subjects were divided into two groups. The first group consisted of patients with POR who received GH and the second group consisted of patients with POR who did not receive GH during a mini-stimulation protocol. On the first group, 8 IU of GH was given from day 1 of stimulation until stimulation was stopped. GnRH antagonist was used to suppress ovulation.

Patients came on the first or second day of their menstrual period, and the level of basal hormone (AMH, FSH, and LH) was checked and transvaginal ultrasound was done to determine the number of antral follicles. If the patient met the inclusion criteria of POR, further mini-stimulation protocol was performed by giving 150 mg Clomiphene Citrate (CC) from day 3 to 7 of their menstrual period. In this study two groups were observed, the first group comprised of patients receiving 8 IU subcutaneous GH injection from day 3-10 in accordance with the start of the injection of CC and the other group was the patients who did not receive GH injection at all.

On days 8, 9, and 10 of menstrual period, 150 IU HMG and 0.25 cc Cetrotide injection (GnRH antagonist) was given at night. Transvaginal ultrasound was performed on day 11 to measure the size of the follicles. If any follicle was found to be ≥18 mm, then the administration of GH can be stopped and ovulation is triggered by the injection of 250 μg ovidrel at night. If there is no follicle sized ≥18 mm, then HMG and GH injections were continued until the trigger is performed.

Ovum pick-up was performed 36 hours after trigger with ovidrel injection. Three days after ovum pick up embryo transfer was performed, but if embryo transfer was not possible (considering the patient's condition), the embryo was vitrified. After embryo transfer, Crinone can be given once daily for luteal support for the next 16 days and 1500 IU Pregnyl injection was given on day 4 and day 7. On day 16, serum ß-hCG evaluation was performed to confirm pregnancy.

RESULTS

The incidence of POR is 15% in all patients in the Morula IVF Clinic, Jakarta during the study period (January 2012 to June 2013). From these patients, 84 cycles met the inclusion criteria, but only 51 cycles were entered in the study and the other 33 cycles were not, 39% due to no fertilization and 61% no oocyte was obtained.

This study includes 51 cycles from women who are classified into two groups; younger than 40 years old (mean=36.5, SD=2.65) and 40 years old and older (mean=42.3, SD=1.67). Most of the subjects (90.2%) had primary infertility, which was caused by endometriosis (27.5%), idiopathic (27.5%), sperm abnormalities (23.5%), mixed cause (13.7%), tubal problems (3.9%), and adenomiosis (3.9%). There was no significant difference in terms of endometrial thickness on the day of hCG triggering, AMH level and stimulation characteristic between both groups. These subjects were divided into two groups, with 29 patients receiving GH and 22 patients without GH. In patients ≥40 years old, the total GH used was found to be higher compared to patients <40 years old, because it takes larger doses (94.50 IU, SD=36.28 IU versus 76.95 IU, SD=12.52 IU) and longer time (11.55, SD=4.61 days versus 9.76, SD=1.72 days) to reach mature follicle size. The use of HMG is also higher in patients ≥40 years old (982.14, SD=691.46) compared to patients <40 years old (714.19, SD=258.37). The patient and stimulation characteristics are further elaborated in Table 1.

Table 1. Patient and Stimulation Characteristics of the Additional Growth Hormone in Mini-stimulation Protocol-Treated Poor Ovarian Responders

	All cycles	< 40 years	≥ 40 years
Number of cycles (%)	51 (100%)	14 (27.5%)	37 (72.5%)
Patient Characteristics			
Age (SD) [years]	40.69 (3.3)	36.5 (2.65)	42.3 (1.67)
Duration of infertility (SD) [years]	8.96 (3.97)	6.71 (3.63)	9.81 (3.8)
Infertility Type			
Primary (%)	46 (90.2%)	13 (92.9%)	33 (89.2%)
Secondary (%)	5 (9.8%)	1 (7.1%)	4 (10.8%)
Infertility cause			
Idiopathic (%)	14 (27.5%)	5 (35.7%)	9 (24.3%)
Tubal problem (%)	2 (3.9%)	0 (0%)	2 (5.4%)
Sperm abnormality (%)	12 (23.5%)	5 (35.7%)	7 (18.9%)
Adenomiosis (%)	2 (3.9%)	0 (0%)	2 (5.4%)
Endometriosis (%)	14 (27.5%)	3 (21.4%)	11 (29.7%)
Mixed (tubal and sperm problem; endometriosis and sperm problem; endometriosis and tubal problem)	7 (13.7%)	1 (7.1%)	6 (16.2%)
Endometrial thickness on the day of hCG	7.25 (1.84)	7.07 (1.9)	7.32 (1.84)
triggering (SD) [mm]			
Mean AMH (SD) [ng/ml]	0.42 (0.39)	0.49 (0.49)	0.39 (0.35)
Stimulation Characteristics			
Stimulation duration (SD) [days]	10.25 (2.88)	9.76 (1.72)	11.55 (4.61)
Stimulation units of GH (SD) [IU]	81.79 (22.47)	76.95 (12.52)	94.50 (36.28)
Stimulation units of hp-HMG (SD) [IU]	787.75 (432.38)	714.19 (258.37)	982.14 (691.46)
Growth hormone use			
Yes (%)	29 (43.1%)	8 (57.1%)	21 (56.8%)
No (%)	22 (56.9%)	6 (42.9%)	16 (43.2%)

No difference was observed in the number of oocytes retrieved (2.21 versus 2.64) and number of embryos transferred (1.24 versus 1.68) in the GH versus the without GH groups. In patients older than 40 years old, GH showed a 4-fold increase of likelihood in producing top quality embryos (OR=3.6; p=0.05). Top quality embryo was determined based on the 2013 Istanbul criteria where day-3 embryo (68 ± 1 hour post-insemination) would have at least 7 equally proportional sized blastomere, with <10% fragmentation.[10] Total clinical pregnancy rate was 17.6%. No significant difference was identified in pregnancy and ongoing pregnancy rate in both groups (17.2% versus 18.2%) and (13.8% versus 13.6%). Miscarriage rate is lower in the GH group, either after positive hCG (25% versus 33%) or after ongoing pregnancy (12 weeks) (20% versus 25%), as presented in Table 2.

Table 2. Ovarian Response and Reproductive Outcome

	All Cycles (n=51)	GH (n=29)	Non-GH (n=22)	*p*-value
Age				
< 40 years	14 (27.5%)	8 (27.6%)	6 (27.3%)	1.00
≤ 40 years	37 (72.5%)	21 (72.4%)	16 (72.7%)	
Number of oocyte retrieval (mean, SD)	2.39 (1.36)	2.21 (0.86)	2.64 (1.81)	0.31
Embryo transfer and quality				
Number of embryo transferred (mean, SD)	1.43 (0.97)	1.24 (0.87)	1.68(1.04)	0.11
Cycles with top quality embryo (%)	20 (39.2%)	15 (51.7%)	5 (22.7%)	0.05*
< 40 years	4 (20%)	2 (6.9%)	2 (9.1%)	
≥ 40 years	16 (80%)	13 (44.8%)	3 (13.6%)	
Number of frozen embryo (mean, SD)	0.39 (0.82)	0.45 (0.78)	0.32(0.89)	0.56
Outcome per embryo transfer				
Positive hCG	9 (17.6%)	5 (17.2%)	4 (18.2%)	1.00
Ongoing Pregnancy	7 (13.7%)	4 (13.8%)	3 (13.6%)	1.00
Miscarriage Rate	22%	20%	25%	
Positive hCG		25%	33%	
Ongoing Pregnancy		20%	25%	

** OR = 3.6*

DISCUSSION

Many treatments in patients with POR are by the use of adjuvant therapy; including GH, DHEA, aspirin, steroids, verapamil, atosiban, testosterone, melatonin and various vitamins. From a variety of adjuvant therapy, GH apparently showed significant results in patients with POR.

Only 9-24% POR patients can undergo ovarian stimulation due to unfavorable response to the stimulation, so that adjuvants are necessary to improve these patients' response to stimulation. Furthermore, at the age of 40, the pregnancy rate (ongoing pregnancy rate) is only 7% in patients with normal stimulation response. To overcome this problem, we need adjuvant therapy.

The findings of this study demonstrated that from 51 subjects who underwent mini-stimulation protocol; where 29 subjects received GH and the other 22 subject did not; there is no significant difference in the number of oocyte retrieval and embryo quality. But if we divide the subjects by age, with a cutoff point of 40 years old, GH showed a 4-fold likelihood in producing top quality embryos (44.8%) in women older than 40 years of age compared to women younger than 40 years old (6.9%). There is also no significant difference in the pregnancy rate in both groups, which may be due to the higher occurrence of aneuploidy in the above 40 years age group.

Miscarriage rate in the group who received GH was lower. Miscarriage rate after positive hCG on GH group is 25% compared to 33% in the non-GH group, and miscarriage rate after ongoing pregnancy (12 weeks) in GH group is 20% compared to 25% in the non-GH group. The use of CC on mini-stimulation protocol did not alter endometrial thickness in both age groups. In patients over 40 years of age, the usage of GH and HMG dose will be higher because it takes larger doses and longer time to reach mature follicle size.

This result is consistent with theories that the older the age of a woman, the higher the amount of cell damage, which caused decreasing quality and

quantity of oocytes/eggs produced. Therefore, according to Bologna criteria they can be considered as poor ovarian responders. This study shows that additional GH on mini-stimulation protocol is effective to produce better quality embryos, even though it was not proven to be significant by reaching a higher pregnancy rate.

Limitations of this study include the retrospective nature of the methodology used, so that the bias that may occur cannot be removed. The number of subjects should preferably be greater so that the results achieved can be more representative of the general population. In the future we hope there will be a study with RCT methodology carried out, to obtain better significance.

CONCLUSION

CC-HMG regimen in mini-stimulation protocol is an effective option in poor ovarian responders. Additional GH in mini-stimulation program provided higher number of top quality embryos in women older than 40 years old, although there were no differences in clinical or ongoing pregnancy rate. Therefore, administration of 8 IU GH since day 1 of stimulation until completion of stimulation can still be considered, especially in women older than 40 years of age.

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