INAJOG

Indonesian Journal of Obstetrics and Gynecology

Volume: 4, No. 4, page 177-240 October 2016

Editorial

Research Article

EDITORIAL

Family Planning Problem in Indonesia

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According to the world population data sheet in 2015, Indonesia was the 4th largest population country in the world with 256 million people.[1] By total fertility rate 2.6, there will be 310 millions of Indonesian people in 2035. Large population represents serious threat, as over-population is the root of environmental problems, such as unsanitary living conditions, the depletion of resources, environmental pollution, and also poverty.

One of the prerequisites for improving Indonesian people's quality of life is through balancing the population growth by controlling the quantity of population. One of the ways is through family planning. Stated at Act No. 52 of 2009 on population and family development, the family construction is the foundation to create the quality family who lives in a healthy environment.[2] This law supports family planning program as a part of efforts to control the pregnancy by using contraceptives.

There are some problems in family planning program. Firstly, the contraceptive prevalence rate did not increase significantly from 60.3% in 2002 to 61.4% in 2007. It remained constant to 61.9% in 2012. Secondly, the total fertility rate (TFR) in same period is only slightly decreased from 3.0 to 2.6. Among ASEAN countries, Indonesia ranked the number six for the lowest fertility rates. Therefore, we still need more effort to earn better result in family planning program.[3]

The reason behind this phenomenon is the use of Non-LTCM (Long-Term Contraception Method) higher than LTCM. Non-LTCM, which has a duration of 1-3 months, shows higher dropout rate (25-41%). Long Term Contraceptive Method ranging from 3 to 5 years of use provides higher chance for survival; however, the number of users are lower than Non-LTCM. This may be caused because the use of this method requires more complex action and skills of health professionals.[4]

Long-term contraception method (LTCM), such as IUD and Implant can be used for the spouse of fertile age that planned to delay the pregnancy; meanwhile, sterilization is used for spouse who planned to stop the fertility.[5]

Implant is a contraceptive containing Levonorgestrel wrapped in capsules silastic silicone (polidemtsilixane) and implanted under the skin. Implant has long service life, release stable low dose hormone, and has reversible effect for the women fertility. The successful rate of this implant contraceptive is high, nearly 100%.[5]

There are some types of implant contraception that available in Indonesia, those are Norplant that has six small silicone rods, Jadelle or Indoplant that has two rods. However, study about effectiveness between those types of implant in Indonesia is still not available. Therefore, in this edition, we try to compare the effectiveness of 2 and 6 rods of implant as contraceptive methods.

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Research Article

The Characteristics of Preeclampsia with Severe Features

Karakteristik Preeklamsia dengan Tanda Perburukan

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Abstract

Objective: To describe the characteristics of preeclampsia with severe features and their risk factors.

Method: This study was a retrospective medical record review of demographic characteristics, obstetric and medical data of preeclampsia with severe features in Dr. Cipto Mangunkusumo Hospital from July to December 2014.

Result: There were 1,013 deliveries which 183 patients of them were diagnosed as preeclampsia with severe features (18.06%). The study showed 67.76% were 20 - 35 years old, most of them were multiparity, and 41.53% were preterm labor with 28 - 33^6 weeks of gestation then followed by 24.59% were 34 - 36^6 weeks' gestation. Majorities of preeclampsia with severe features patients were without complication either to the mother or the baby. There were 1 case of maternal mortality and 15 cases of intra uterine fetal death (IUFD). There were 73.77% cases delivering by cesarean section. The complication of the mother in preeclampsia with severe features was related significantly to the complication in baby, such as preterm delivery. Besides, women's age and parity had significant relationship with baby complication.

Conclusion: There is association of complication in preeclampsia with severe features women with baby, namely preterm delivery. Besides, women's age and parity is related to complication of baby.

[Indones J Obstet Gynecol 2016; 4-4: 179-182]

Keywords: complication, preeclampsia, risk factors

Abstrak

***Tujuan**: Untuk mendeskripsikan karakteristik preeklamsia dengan tanda perburukan dan faktor risikonya.*

***Metode**: Penelitian ini merupakan penelitian retrospektif mengenai karakteristik preeklamsia dengan tanda perburukan pasien-pasien obstetri dan ginekologi di RS Dr. Cipto Mangunkusumo dari bulan Juli 2014 sampai Desember 2014.*

***Hasil**: Terdapat 1013 total persalinan selama studi dilakukan, dan di antaranya terdapat 183 (18,06%) kasus preeklamsia dengan tanda perburukan. Dari penelitian ini didapatkan 67,76% pasien berada di rentang umur 20-35 tahun dan mayoritas dari pasien tersebut adalah multiparitas; dan 41,53% adalah persalinan preterm pada 28-33^6 minggu gestasi dan diikuti 24,59% persalinan preterm pada 34-36^6 minggu gestasi. Mayoritas pasien dengan preeklamsia dengan tanda perburukan tidak mengalami komplikasi, baik pada ibu maupun bayinya. Didapatkan pula 1 kematian maternal dan 15 kematian fetus dalam rahim. Terdapat sekitar 73,77% kasus yang dilahirkan melalui seksio sesarea. Preeklamsia dengan tanda perburukan dengan komplikasi secara signifikan berhubungan dengan persalinan preterm. Selain itu, usia maternal dan status paritas dengan preeklamsia dengan tanda perburukan dan komplikasi terhadap bayi.*

***Kesimpulan**: Preeklamsia dengan tanda perburukan dengan komplikasi secara signifikan berhubungan dengan persalinan preterm. Selain itu, umur maternal dan status paritas secara siginifikan berhubungan dengan preeklamsia dengan tanda perburukan dan komplikasi terhadap bayi.*

[Maj Obstet Ginekol Indones 2016; 4-4: 179-182]

***Kata kunci**: faktor risiko, komplikasi, perburukan, preeklamsia*

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INTRODUCTION

Maternal mortality is a health indicator which describes the condition of its country. It shows the very wide gap between rich and poor, urban and rural areas among countries in the world. World Health Organization (WHO) attempts to reduce the maternal mortality rate (MMR) around the worlds, including Indonesia through Millennium Development Goals (MDGs) continued by Sustainable Development Goals (SDGs).[1] Based on data from Indonesia Department of Health, preeclampsia is one of three commonest cause for maternal death.[2] Preeclampsia is defined as a syndrome consisting of hypertension with blood pressure more or equal to 140/90 and/or proteinuria more or equal to positive 1. These signs are appeared at 20 weeks of gestational age and resolved at 12-week postpartum. While, preeclampsia with severe features is known as hypertension with blood pressure more or equal to 160/110 and/or proteinuria more or equal to positive 2. The onset is similar to preeclampsia. The risk factors for preeclampsia are multifactorial. Several risk factors which have been identified are molar pregnancies, nulliparity, aged less than 20 years old or over 35 years old, more

than one fetus, chronic hypertension, diabetes mellitus and renal disease. Besides, preeclampsia is also influenced by parity, genetic, and environmental factors.[1,3]

The incidence of preeclampsia was relatively stable between 4 and 5 cases per 10,000 live births in developed countries. In the developing countries, the incidence of preeclampsia was around 3.9%. Meanwhile, in Dr. Cipto Mangunkusumo hospital as the center of referral hospital in Indonesia, the incidence in 2008-2009 was 16.3%.[4] The MMR was varied from 0% to 4%. Increased maternal death due to complications involves various body systems, such as intracerebral hemorrhage and pulmonary edema. Preeclampsia has also an impact for the baby ending to the infant death. The perinatal mortality rate was ranged from 10% to 28%. Prematurity, growth retardation, and increased risk of abruption placenta often cause the perinatal death. Approximately less than 75% eclampsia occurs antepartum and 25% in the postpartum. Almost all cases (95%) antepartum eclampsia are happened in the third trimester.[5]

The incidence of preeclampsia occurs on 5% population of white women, 9% population of women Hispanic, 11% in women African-American. The incidence on nullipara reaches 3-10%, maternal weight affects the risk of preeclampsia from 4.3 to 13.3%.[6] Women with preeclampsia in their first pregnancy have a greater risk to be preeclampsia in the next pregnancy. Smoking during pregnancy is associated with reduced risk of hypertension in pregnancy.[6] Therefore, this study aims to describe the characteristics of preeclampsia with severe features and their risk factors

METHODS

This study was a retrospective medical record review about preeclampsia with severe features in Dr. Cipto Mangunkusumo Hospital. All preeclampsia with severe features records between July and December 2014 were collected and reviewed. We did the statistical analysis using SPSS software. We used chi square to determine the relative risk between several independent variables and fetal complication.

Table 1. The Characteristics of Preeclampsia with Severe Features in Dr. Cipto Mangunkusumo Hospital

Characteristics		N	%
Age (years old)	<20	10	5.46
	20 - 35	124	67.76
	>35	49	26.78
Parity	<1	63	34.43
	2 - 5	120	65.57
	>5	0	0
Gestational Age (weeks)	20 - 27^6	8	4.37
	28 - 33^6	52	28.42
	34 - 36^6	45	24.59
	37 - 41^6	76	41.53
	>=42	2	1.09
Maternal Complication	None	144	78.69
	HELLP syndrome	27	14.75
	Eclampsia	7	3.83
	HELLP syndrome and Eclampsia	5	2.73
Fetal Complication	None	151	82.52
	IUGR	19	10.38
	Poor APGAR score	10	5.46
	IUGR and Poor APGAR score	3	1.64
Maternal Mortality	Life	182	99.45
	Dead	1	0.55
Fetal Mortality	Life	168	91.80
	Dead	15	8.20
Mode of Delivery	Vaginal	48	26.23
	Cesarean section	135	73.77

RESULTS

There were 183 cases of preeclampsia with severe features among 1,013 pregnant women recorded coming to Dr. Cipto Mangunkusumo hospital at Emergency Unit. The majority of preeclampsia with severe features cases was among 20-35 years old and multiparity (65.57%). Almost half of women (41.53%) were in term gestational age, followed by 28 - 36^6 weeks of gestation around 28.42%, and 24.59% women was in 34 - 36^6 weeks of gestation. The majority of preeclampsia with severe features cases had no complication either the mother or the baby; there were only 27 cases having HELLP syndrome, 7 cases with eclampsia, and 5 cases with both HELLP syndrome and eclampsia. In term of baby complication, only 17.48% baby were born with complication consisting of intrauterine growth retardation (IUGR), poor APGAR score, IUGR and APGAR score in each percentage of 10.38%, 5.46%, 1.46%; respectively. In this study, there was one maternal death with the characteristics of less than 20 years old, primigravida, at term of gestation with HELLP syndrome and lung edema. The baby was delivered by cesarean section having poor APGAR score. Besides, there were 15 intrauterine fetal death (IUFD) cases. Meanwhile, around 73.77% preeclamptic women with severe features were delivered by cesarean section.

Table 2 showed that there was significant association between fetal and maternal complication of preeclampsia with severe features.

Based on statistics, maternal age had significant relationship with fetal complication; whereas, young maternal age (<20 years old) had a tendency of increasing 2.2 times risk to have fetal complication (shown in Table 3).

Table 4 depicted that there was significant association between parity and fetal complication; whereas, nulliparity was considered as the risk factor for the complication.

Table 2. Relationship between Fetal and Maternal Complication of Preeclampsia with Severe Features

Maternal Complication	Fetal		Total	RR	CI 95%	p-value
	With Complication	Without Complication				
With	12	27	39	2.215	0.035-0.303	0.014
Without	20	124	144	1		
Total	32	151	183			

Table 3. Relationship between Fetal Complication and Maternal Age

Maternal Age	Fetal		Total	RR	CI 95%	p-value
	With Complication	Without Complication				
< 20 years old	4	6	10	2.156	0.004-0.481	0.050
20 - 35 years old	23	101	124	1		
> 35 years old	5	44	49	0.55	0.026-0.224	0.118
Total	32	151	183			

Table 4. Relationship between Fetal Complication and Parity

Parity	Fetal		Total	RR	CI 95%	p-value
	With Complication	Without Complication				
With	17	46	63	2.158	0.014-0.03	0.014
Without	15	105	120	1		
Total	32	151	183			

DISCUSSION

The number of preeclampsia with severe features patients who came to Dr. Cipto Mangunkusumo hospital from July to December 2014 were 183 women of 1,013 pregnant women. The percentage was around 18.06%. Compared with the period of 2008-2009 which was only 16.3%, it meant that there was an increasing around 2% within 5 years.[4] It might be caused by the deterioration of the pregnant women's health condition in Jakarta. Apart from that, in the era of national health coverage (*Jaminan Kesehatan Nasio-nal* JKN), there is an increasing awareness of people to seek treatment at health center so that the number of diagnosed case, especially preeclampsia raise in hospital.

Of the characteristics, the dominance of women's age was between 20 and 35 years old (67.76%) and certainly, the number of maternal and fetal complication due to preeclampsia were dominant in that age group, such as HELLP syndrome (70.37%), eclampsia (85.71%), 80% for both eclampsia and HELLP syndrome. While, the fetal complication consisting of IUGR, poor APGAR score, IUGR with poor APGAR score was 73.68%, 60%, 100%; respectively in the age group of 20-35 years old. Although maternal age was not significantly associated with complication of preeclampsia with severe features, the women less than 20 years old had a tendency for complication of preeclampsia with severe features about 1.2 times greater than the maternal age of 20-35 years old. Besides, maternal age had a significant relationship with fetal complication; whereas, women less than 20 years old tended to increase 2.2 times of fetal complication. It is quite reasonable according to the habit in capital city, a lot of women postpone their pregnancy for the career.

Pregnancy in any parity group should be noticed to be preeclampsia. Based on statistical calculation, the result showed there was no association between parity and maternal complications in preeclampsia, although parity was related to fetal complication. This might occur due to other factors that have more influence on pregnant women than only a parity.

From the study, most of women were at term gestational age. There were probably due to lack of awareness among pregnant women for doing antenatal care (ANC) or lack of screening facility in the primary health services. Preeclamptic patients who came to the emergency unit on Dr. Cipto Mangunkusumo hospital were generally without complications. The complication of preeclampsia with severe features were HELLP syndrome (14.57%), eclampsia (3.82%) and both HELLP syndrome and eclampsia (2.73%). Statistical analysis showed that preterm pregnancy complication was related to the incidence of preeclampsia with severe features. The analytic issue was due to the lack of awareness for doing ANC, poor economic society, and the number of children. In women with preeclampsia, the complication could be seen to the dominance of HELLP syndrome at 28-33[6] weeks of gestation as much as 8.74% of the total preeclampsia's incidence.

Preeclampsia caused one maternal death and 15 IUFD in the second semester during 2014. Of the IUFD cases, 12 cases were obtained in women with preeclampsia without complications; while, complication of preeclampsia with HELLP syndrome only caused one IUFD. Eclampsia and HELLP syndrome contributed to 2 patients with IUFD. In linear regression calculation, it was also found that there was no association between complication of preeclampsia and IUFD. Maternal complication of preeclampsia should not be associated with IUFD. Actually, IUFD itself was associated with the prematurity.

CONCLUSION

In Dr. Cipto Manggunkusumo Hospital, there are 183 cases of preeclampsia with severe features among 1,013 patients that come to emergency unit from July to December 2014. Preeclamptic women with severe features are associated with preterm delivery. Apart from that, women's age and parity have significant relationship with severe features preeclampsia and the complication of the baby.

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Research Article

Heat Shock Protein 70 (HSP 70) Level in Threatened Abortion

Kadar Heat Shock Protein 70 (HSP 70) pada Abortus Iminens

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Abstract

Objective: To determine the level of Heat Shock Protein 70 (HSP 70) in threatened abortion compared with normal pregnancy.

Method: This was a cross-sectional analytic study design conducted to examine the HSP 70 level on 25 subjects of pregnant women with <20 weeks of gestation and 30 subjects with threatened abortion. It was held at Obstetrics outpatient clinic Prof. dr. RD Kandou Manado Hospital. The data obtained were analyzed using SPSS software version 22.0 and we did the discussion using the existing literature theory.

Result: The statistical analysis using the Mann-Whitney test showed that there were significant differences of median level of HSP 70 between threatened abortion group and normal pregnancy with less than 20 week of gestation (p<0.001).

Conclusion: Heat Shock Protein 70 can be a marker to predict the risk of miscarriage in the first trimester of pregnancy.

[Indones J Obstet Gynecol 2016; 4-4: 183-186]

Keywords: HSP 70, pregnancy, threatened abortion

Abstrak

***Tujuan**: Mengetahui perbandingan kadar Heat Shock Protein 70 (HSP 70) pada abortus iminens dibandingkan dengan kehamilan normal.*

***Metode**: Penelitian potong lintang analitik secara komparatif dilakukan dengan memeriksa kadar HSP 70 pada 25 wanita hamil dengan usia kehamilan kurang dari 20 minggu dan 30 subjek dengan abortus iminens. Penelitian ini dilakukan di unit rawat jalan Obstetri RS Prof. dr. RD Kandou Manado. Kami melakukan analisis dengan SPSS versi 22,0 dan diskusi menggunakan teori literatur yang ada.*

***Hasil**: Dari analisis statistik dengan menggunakan Uji Mann-Whitney menunjukkan terdapat perbedaan yang bermakna pada kadar HSP 70 antara kelompok aborsi iminens dengan kehamilan normal kurang dari 20 minggu (p<0,001).*

***Kesimpulan**: Heat shock protein 70 dapat menjadi marker untuk memprediksi risiko abortus pada trimester pertama kehamilan.*

[Maj Obstet Ginekol Indones 2016; 4-4: 183-186]

***Kata kunci**: abortus iminens, HSP 70, kehamilan normal*

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INTRODUCTION

Pregnancy is one of frightening events for old couple because many complications often occur on that age.[1] Threatened abortion as one of complications is a bleeding happening less than 20 weeks of gestation. It can continue for several days or recur and it is usually accompanied by slight pain on the lower abdomen or back pain as like the menstrual period.[1] Currently, around 15% of women experience the spontaneous abortion at the conception; however, most of it occur without realizing of it. Meanwhile, 15-20% cases ended with spontaneous abortion or ectopic pregnancy.[2] More than 80% of abortion happen in the first trimester of gestation up to 14-week gestational age.[1] Apart from that, abortion can also be caused by the imbalance between oxidants and anti-oxidants in uteroplacental; whereas, this balance has an important role in various diseases including abortion.

Cells undergoing environmental stress will encounter the heat shock response (HSR). This response mechanism will involve cell protection called as heat shock protein (HSP) to help an organism dealing with the environmental pressure.[3] The role of other cellular processes to oxidative stress is called as an ischemic condition. Therefore, member of HSP 70 and co-chaperones play an essential role to sort and control the protein quality through selecting and directing protein to the proteasome. As known, the proteasome has function to disintegrate of damage protein and HSP assists its function.

Heat shock protein is a conservative primary structure of polypeptide which depends on molecular weight. It can be divided into macromolecule (HSP 100 and HSP 90), medium molecule (HSP 70, HSP 60, and HSP 40), and the low molecule (HSP 27 and HSP 10).[4] Many studies stated that

HSP 70 influences in variety diseases, such as heart disease, cancer, acute infection, asthma, and pathological pregnancy. Heat shock protein 70 also plays a role in embryogenesis and reproductive cycle. Extracellular protein of HSP 70 is able to induce pro inflammatory immune response (Th1).[2] Actually, the concentration level of HSP 70 decreases in normal pregnancy. The HSP 70 presents in the peripheral circulation of normal pregnancy. In the meantime, its concentration will decrease as the increase of gestational age. However, it has negative correlation to maternal age. Decreasing level of HSP 70 may lead to the immunological tolerance process to the fetus. Indeed, HSP 70 concentration level is associated with an increased risk of some pregnancy complications.[3]

Intracellular expression of HSP 70 can lead to other obstetrical complications, namely abortion. The HSP 70 in syncytiotrophoblast between 8 and 9 week-gestational age will increase sharply. Meanwhile, the increase of HSP 70 from placenta in the first trimester indicates the miscarriage process. In addition to that, the increase level of HSP 70 on lymphocytes is associated with high risk pregnancy as it signs early onset of pregnancy failure.[4] Although intracellular HSP 70 has anti-inflammatory effect, extracellular HSP 70 may act as stress signal molecule from non-physiological condition, such as cellular stress or damage, simultaneously with pro inflammatory cytokines both innate or adaptive response. Extracellular HSP 70 binds to surface receptors (CD14, CD36, CD40, CD91, LOX-1, Toll-like receptor 2 and 4) on the Antigen Presenting Cell (APC) and stimulates the proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL-1β and IL-6), chemokines, and nitric oxide production, as well as expression of molecules. The role of cytokines in the inflammatory reaction in whole process is a response to eliminate inflammation.[5,6]

According to the theory, in the first trimester, the placenta will filtrate the maternal blood; thus, the plasma level of HSP 70 will increase in miscarriage pregnancy compared with normal pregnancy. This study aims to determine the level of HSP 70 in threatened abortion compared with normal pregnancy.

METHODS

This was an analytic observational using cross sectional study design. We held the study by recruiting all pregnant women coming to Obstetrics outpatient clinic at Prof. dr. RD Kandou Manado Hospital from February to April 2016.

The inclusion criteria were women with threatened abortion and normal pregnancy with gestational age less than 20 weeks. The collection of samples was calculated by using a single average formula. After calculating, the minimal samples consisted of 16 threatened abortion women and 16 normal pregnancy with <20 weeks of gestation. We excluded all women with molar pregnancy, abnormalities of the uterine, myoma uterine, gestational diabetes mellitus, and pregnancy-induced hypertension.

We examined the level of HSP 70 from subjects' blood through ELISA in Manado Prokita laboratory. We did the analysis using Mann-Whitney test to assess the mean level of HSP 70 on imminent abortion group compared with normal pregnancy. The data obtained were processed using the software program of Statistical Product and Service Solution (SPSS) for Windows version 22.0.

RESULTS

During the study, we collected 55 subjects of pregnant women. Table 1 showed the characteristics of subjects in this study. Actually, only age and gestational age had normal distribution between threatened abortion and normal pregnancy group ($p>0.05$) based on Kolgomorov-Smirnov test. Meanwhile, the other characteristics did not describe normal distribution between the groups.

Table 2 indicated the average level serum of HSP 70 between the groups. In threatened abortion group, the mean, SD, median, and min-max were 1.5, 0.3, 1.4, and 1.1-2.2 pg/ml; respectively. Meanwhile, we obtained serum level of HSP 70 in normal pregnancy group with the mean (SD) of 0.3 (0.1) pg/ml and median (min-max) of 0.3 (0.2-0.4) pg/ml.

Through using non-parametric statistical test of Mann-Whitney, we got the significant difference ($p<0.001$) of the median level of HSP 70 between threatened abortion and normal pregnancy groups. Therefore, the concentration of HSP 70 was associated with the occurrence of threatened abortion.

DISCUSSION

Table 1 described the 55 subjects recruited in this

Table 1. The Characteristics of Subjects

Characteristics	Theatened Abortion		Normal Pregnancy	
	N	(%)	N	(%)
Age (years old)*				
18-23	9	30	10	40
24-29	11	37	10	40
30-34	10	33	4	16
35-39	0	0	1	4
History of miscarriage				
Never	19	63	18	72
1 times	5	17	5	20
≥ 2 times	6	20	2	8
Education				
Elementary	0	0	0	0
Middle School	0	0	1	4
High School	29	97	24	96
Undergraduate	1	3	0	0
Smoking				
Yes	1	3	0	0
No	29	97	25	100
Gestational age*				
0-6 weeks	0	0	0	0
6-12 weeks	18	60	12	48
12-20 weeks	12	40	13	52

**Normal distribution (p>0.05)*

Table 2. The Level Serum of HSP 70

Group	N	HSP 70 levels (pg/ml)				p
		Mean	SD	Median	Min-max	
Threatened Abortion	30	1.5	0.3	1.4	1.1 - 2.2	< 0.001
Normal pregnancy	25	0.3	0.1	0.3	0.2 - 0.4	

study. Women on 24-29 years old (37%) were the largest age group for threatened abortion; while, both 18-23 and 24-29 years old (40%) were the largest group for normal pregnancy. This study showed there was not association between age and incidence of abortion. Based on study by Baqur AS, et al. in India, they explained that between 24 and 29 years old was the highest group for miscarriage in 2013.[7] Meanwhile, Tan Hao study in China stated the average group of women undergoing miscarriage was 26 years old in 2007.[8] From our study, we got that 63% of threatened abortion group was never experienced miscarriage and 72% of normal pregnancy did not have history of miscarriage. Study by Lena L, et al. in Poland, there was significant relationship between level of HSP 70 and history of recurrent miscarriage on threatened abortion group.[9] Of educational level, we found the incidence of threatened abortion and normal pregnancy was more common on high school (97% and 96%). According to smoking history, we found that almost all subjects never had smoking habit. Study by Hao Tan, et al. in 2007 concluded there was significantly different between smoking habit and abortion in China.[8] Based on gestational age, we found that the prevalent in 6-12 weeks of gestation (60%) and <20 weeks of gestation (52%) for normal preg-

nancy group. According to the study by Xiangjun Gong, et al. in 2012, they found the most frequent of abortion happened in 6-12-week-gestational age because women felt anxiety and depression in the first trimester.[10] Meanwhile, Adams, et al. through their study in 2007 stated that miscarriage in the first trimester is usually caused by fetal factors; whereas, 20% of them are due to fetal abnormalities.[11]

Table 2 indicated that the mean level of HSP 70 in threatened abortion group was 1.51 (SD 0.3) pg/ml with a median level of 1.4 (1.1-2.2) pg/ml. While, the level of HSP 70 in normal pregnancy group was 0.3 (SD 0.1) pg/ml with a median level of 0.3 (0.2-0.4) pg/ml. Based on study by Baqur AS, et al. in India, the mean level of HSP 70 in threatened abortion group was from 1.06 to 1.54 pg/ml.[7] Our result was not too different from Molvarec, et al. in Hungary, they got the mean level of HSP 70 in normal pregnancy was between 0.27 and 0.39 pg/ml.[12]

The non-parametric statistical test using Mann-Whitney showed the significant difference of HSP 70 medial level between threatened abortion and normal pregnancy group ($p<0.001$). It meant that the HSP 70 had association with abortion. Tan Hao based study in China said that there was positive correlation between HSP 70 and miscarriage.[8] In contrary to the result, Lena N, et al. in Poland through their study concluded that there was no significant relationship in HSP 70 on both miscarriage and normal pregnancy group. The reason was due to the limitation of smaller sample and they took the sample at 6 weeks' post abortion which might influence the result.[9]

Increased level of HSP 70 in the blood circulation was considered not only as marker of pathological processes, but also having important role in the pathogenesis of abortion. According to Jauniaux, et al. in 2003, they stated that the increased expression of HSP 70 in the placenta at the first trimester caused the miscarriage and it had an essential role to the abortion process.[4] Meanwhile, according to Hao Tan in 2007, the level of HSP 70 on lymphocytes found to be associated with the risk of pregnancy; however, it was not good as the marker for the first trimester of pregnancy.[8] Meanwhile, Koga, et al. in 2010 through their study said that HSP 70 could occupy the extracellular toll-like receptor (TLR) inducing proinflammatory cytokines, including IL-1β, IL-6 and TNF-α. These cytokines would further cause the abortion.[13]

CONCLUSION

Heat Shock Protein 70 can be a marker to predict the risk of miscarriage in the first trimester of pregnancy.

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Research Article

Effect of Rectal Misoprostol to Blood Loss at High Risk Pregnancy

Efek Pemberian Misoprostol Per-rektal terhadap Jumlah Perdarahan pada Kehamilan Risiko Tinggi

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Abstract

Objective: To compare the effectiveness of rectal misoprostol administration to the amount of blood loss in 4th stage of labor at high risk pregnancy.

Method: We recruited all pregnant women with high risk criteria including anemia, age ≥ 35 years old, or the number of pregnancies ≥ 4. Women would deliver appropriate to standard procedure of normal delivery. After that, we gave 400-mcg tablet of misoprostol rectally in treatment group. To count the amount of blood loss during 4th stage of labor, we put the underpad.

Result: The amount of blood loss in 4th stage of labor in the treatment group was 201.1 (SD 80.3) ml less than the control group (285.9 (SD 93.2) ml). The result showed that the administration of 400-mcg misoprostol tablet rectally immediately after the birth of the placenta at high risk pregnancy impacted significantly to reduce the amount of blood loss in 4th stage of labor (p<0.001). The incidence of post-partum haemorrhage in the treatment group was 3.3% and 10% in control group. The drug side effects complained were nausea (6.7%) and shivering (3.3%).

Conclusion: Administration of 400 mcg rectal misoprostol after delivering the placenta in high risk pregnancy has significant influence to reduse the amount of blood less in fourth stage of labor.

[Indones J Obstet Gynecol 2016; 4-4: 187-189]

Keywords: 4th stage of labor, misoprostol, rectal, the amount of blood loss

Abstrak

***Tujuan**: Untuk membandingkan jumlah perdarahan kala IV persalinan yang diberikan misoprostol per rektal segera setelah lahirnya plasenta pada kehamilan risiko tinggi.*

***Metode**: Seluruh ibu hamil dengan salah satu kriteria risiko tinggi yang ditetapkan yaitu anemia, usia ≥ 35 tahun, atau kehamilan ≥ 4. Ibu yang akan bersalin tersebut dilahirkan sesuai prosedur Asuhan Persalinan Normal. Pada kelompok perlakuan, setelah lahirnya plasenta, pasien segera diberikan tablet misoprostol 400 mcg per rektal. Tetapi pada kelompok kontrol, tidak diberikan tablet misoprostol. Kemudian diletakkan alas bokong untuk menampung darah yang keluar selama kala IV persalinan.*

***Hasil**: Jumlah perdarahan pada kala IV persalinan kelompok perlakuan yaitu sebanyak 201,1 (SD 80,3) ml, lebih sedikit dibanding dengan kelompok kontrol yaitu sebanyak 285,9 (93,2) ml. Dari hasil uji analisis didapatkan bahwa pemberian tablet misoprostol 400 mcg per rektal segera setelah lahirnya plasenta pada kehamilan risiko tinggi mempunyai pengaruh yang signifikan untuk menurunkan jumlah perdarahan kala IV persalinan (p<0,001). Jumlah perdarahan kala IV ≥500 ml pada kelompok perlakuan yaitu sebanyak 3,3% lebih sedikit dibandingkan dengan kelompok kontrol yaitu sebanyak 10%. Ditemukan efek samping obat pada sebagian kecil sampel berupa mual (6,7%) dan menggigil (3,3%).*

***Kesimpulan**: Pemberian 400 mcg misoprostol per rektal setelah pengeluaran plasenta pada kehamilan risiko tinggi dapat menurunkan jumlah perdarahan pada kala IV persalinan.*

[Maj Obstet Ginekol Indones 2016; 4-4: 187-189]

***Kata kunci**: jumlah perdarahan, kala IV, misoprostol, rektal*

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INTRODUCTION

Postpartum haemorrhage (PPH) is a bleeding occured more than or equal with 500 cc after third stage of labor.[1] Postpartum haemorrhage is one of major pregnancy complication which is happened around 4-6% of vaginal delivery and it becomes the main cause of maternal mortality and morbidity. Each year, it causes 25-43% of maternal mortality during delivery and it is related to 515,000-600,000 cases of pregnancy death worldwide.[1] According to survey conducted by Survey Demografi Kesehatan Indonesia (SDKI) in 2012, the mortality rate in Indonesia was around 359 per 100,000 live births. This rate was increased from 228 per 100,000 live births in 2007.[2]

Uterine atony is the commonest cause of PPH contributing around 70% of PPH cases. It can be occurred right after delivery on both spontaneous or operative vaginal delivery and abdominal delivery.[3] Moreover, uterine atony often becomes the fastest killer for women in less than one hour due to PPH. More than 90% cases of uterine atony

usually happen during the first 24 hours of delivery. Therefore, supervision and prevention of PPH are the main concern.[4,5] In general, 88% of PPH takes place during four hours after delivery and anemia is the risk factor for massive PPH among pregnant women in developing countries.[6]

Clinicians often use some types of prostaglandin in fourth stage of labor to prevent PPH; however, active management of third stage had been properly done. The most often prostaglandin agent used to prevent PPH is misoprostol.[7]

Misoprostol as E1 prostaglandin is stable in high temperature and it can be used orally, sublingually, or even rectally. Misoprostol has been massively used in obstetrics and gynecology cases to induce the labor, management of abortion and PPH.[8] Bamigboye, et al. reported that 400-mcg misoprostol given rectally is effective to prevent the PPH.[9]

This study aims to determine the effect of 400-mcg rectal misoprostol given after delivering the placental to the amount of bleeding in fourth stage of labor for high risk pregnancy.

METHODS

This study was a randomized controlled trial held in delivery room of Dr. Wahidin Sudirohusodo Hospital, Fatimah Mother and Child Hospital, Pertiwi Mother and Child Hospital, Labuang Baji Hospital in Makassar from November 2014 to February 2015. The sample were taken through consecutive random sampling. The number of samples of each group were 30 subject. We recruited the high risk pregnant women and showed anemia through laboratory test (hemoglobin level ≤ 9 g/dl), age ≥ 35 years old, or grandemultipara (≥ 4 pregnancies).

Subjects in study group would immediately be given the 400-mcg rectal misoprostol right after delivering the placenta. Meanwhile, the control group did not get anything. After that, we put the underpad on the subjects' bottom to measure the amount of blood loss during fourth stage of labor. Data taken from this study were written down and further analyzed using SPSS.

RESULTS

There were 60 subjects taken consisted of 30 subjects in each group of control and study.

Table 1 showed that blood loss volume in fourth stage of labor fulfilling the high risk criteria. In study group, the mean of blood loss was around 201.1 (SD 80.3) ml and 285.9 (SD 93.2) ml in control group. Statistical analysis through independent t test showed that there was a significant difference in blood loss volume during fourth stage of labor in high risk pregnancy women (p<0.001).

Table 1. The Effectivity of Rectal Misoprostol in High Risk Pregnant Women Group

Group	Blood Loss (ml)		Discrepancy in Mean	p*
	Mean	SD		
Study group	201.1	80.3	84.8	<0.001
Control group	285.9	93.2		

* *Independent T-Test*

Table 2. The Incidence of Postpartum Haemorrhage

The Amount of Blood Loss in Stage 4 Labor	Study Group N (%)	Control Group N (%)
≥ 500 ml	1 (3.3%)	3 (10%)
< 500 ml	29 (96.7%)	27 (90%)

Table 2 showed that there was only 3 of 30 subjects in control group and 1 of 30 subjects in study group experiencing more than 500 ml blood loss in fourth stage of labor. Table 3 depicted the several side effects from rectal misoprostol including nausea (6.7%) and shivering (3.3%).

Table 3. Side Effects from the Study

Side Effect	Study Group N (%)	Control Group N (%)
None	27 (90%)	30 (100%)
Nausea	2 (6.7%)	0 (0%)
Shivering	1 (3.3%)	0 (0%)

DISCUSSION

This study showed that the amount of blood loss in fourth stage of labor for the whole subjects was 285.9 (SD 93.2) ml in control group and 201.1 (SD 80.3) ml in study group. The difference was occurred due to the rectal misoprostol mechanism of action in study group to reduce the amount of blood loss. The statistical analysis through in-

dependent t test showed there was significantly different between study and control group of blood loss ($p<0.001$). A study by Laili Chilmawati in Yogyakarta described that the amount of blood loss in fourth stage of labor among women who delivered vaginally was 102.13 (SD 67.34) ml in control group. This distinction was happened due to the sample criteria of high risk pregnant women. It made higher incidence of blood loss compared with the study done in Yogyakarta.[10]

The result of this study showed the significant correlation between parity and the amount of blood loss in fourth stage of labor among both study ($p=0.041$) and control group ($p=0.002$). This result revealed that blood loss in fourth stage of labor was mostly influenced by parity as one of risk factors instead of other risk factors. The result of this study was in accordance with the other study; whereas, the parity is claimed as the highest risk of PPH among all others.[11]

The number of subjects with blood loss volume more than 500 ml in fourth stage of labor were 3 (10%) and 1 (3.3%) in control and study group; respectively. This result showed that 400-mcg rectal misoprostol after delivering placenta could reduce the incidence of PPH in high risk pregnancy. Misoprostol is the recommendation agent to prevent PPH which has officially been published by International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO).[8] On the other hand, this study also found several side effects of rectal misoprostol including nausea (6.7%) and shivering (3.3%). In conclusion, the use of 400-mcg rectal misoprostol is safe for the patients.

CONCLUSION

The use of 400-mcg rectal misoprostol right after delivering the placenta in high risk pregnancy has significant influence to reduce the amount of blood loss in fourth stage of labor. Parity as a risk factor is considered the strongest factors contributing the amount of blood loss. The management of PPH with rectal misoprostol after delivering placenta as a prophylactic is recommended for high risk pregnancy. In future, other studies should be conducted to assess the impact of other high risk factors toward blood loss volume in fourth stage of labor.

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Research Article

A Randomized Five-Year Comparative Study of Two Levonorgestrel-Releasing Implant Systems: Norplant® Capsules and Jadena® Rods

Penelitian Komparatif Acak Lima Tahun antara Dua Implan Levonogestrel: Kapsul Norplant© dan Batang Jadena©

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Abstract

Objective: To provide a randomized comparison between Jadena® and Norplant® in terms of efficacy and acceptability among Indonesian women.

Method: This study was a phase IV, open label, randomized, multicenter study throughout Indonesia. Subjects were Indonesian adult women who were randomized to receive Jadena® or Norplant® as their contraceptive method. The subjects were recruited from 6 large cities in Indonesia, such as Medan, Palembang, Jakarta, Semarang, Surabaya, and Makassar.

Result: Of 600 subjects, 301 women getting to Jadena® and 299 women to Norplant® were enrolled between August 1998 and February 1999. The mean age was 29.8 (SD 5.3) years old, ranging from 18 to 40 years old. We did not find the pregnancy during the study. Non-pregnancy probability at the end of one year was similar between Jadena® (0.920 (SD 0.016)) and Norplant® users (0.916 (SD 0.084)). The continuation rates of Jadena® at one and three-year were 95.3% and 66.8%; whereas, the continuation rates of Norplant® was 94.3% at year-1 and 70.2% at year-3.

Conclusion: The new two rod levonorgestrel subdermal system (Jadena®) showed similar efficacy with the old six capsule levonorgestrel subdermal system (Norplant®) in term of birth control. Both implant systems also have similar tolerability profile. Jadena® is easier to insert and remove than Norplant®.

[Indones J Obstet Gynecol 2016; 4-4: 190-197]

Keywords: birth control, efficacy, implant

Abstrak

***Tujuan**: Untuk mengetahui efikasi dan akseptabilitas antara Jadena© dan Norplant© di antara perempuan Indonesia.*

***Metode**: Penelitian ini merupakan fase 4, terbuka, acak, dan multisenter di Indonesia. Subjek penelitian merupakan perempuan dewasa Indonesia yang teracak untuk menerima Jadena© atau Norplant© sebagai metode kontrasepsi. Penelitian ini diambil dari 6 kota besar di Indonesia yaitu Medan, Palembang, Jakarta, Semarang, Surabaya, dan Makassar.*

***Hasil**: Dari total 600 subjek, 301 menggunakan Jadena© dan 299 mengunakan Norplant© pada periode Agustus 1998 hingga Februari 1999. Rerata usia ialah 29,8 (SD 5,3) tahun berkisar antara 18 hingga 40 tahun. Tidak ada kehamilan yang terjadi selama periode observasi. Kemungkinan hamil setelah 1 tahun antara Jadena© (0,920 (SD 0,016)) dan Norplant© (0,916 (SD 0,084)). Angka kebertahanan penggunaan Jadena© pada tahun 1 dan tahun 3 ialah 95,3% dan 66,8%, sementara pada Norplant© ialah 94,3% dan 70,2%.*

***Kesimpulan**: Sistem subdermal levonogestrel 2 batang (Jadena©) memiliki efikasi yang mirip dengan sistem subdermal lama menggunakan 6 kapsul (Norplant©) dalam mengontrol kehamilan. Kedua sistem implan memiliki profil tolerabilitas yang serupa. Jadena© lebih mudah dimasukkan dan dikeluarkan daripada Norplant©.*

[Maj Obstet Ginekol Indones 2016; 4-4: 190-197]

***Kata kunci**: efikasi,implan, kontrol kehamilan*

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INTRODUCTION

Levonorgestrel (LNG) is a synthetic progestin used for contraception either alone or in combination with ethynyl estradiol. The preparation in LNG administered alone is progestin only contraceptive pills (known as mini pills), Norplant® and Jadena® subdermal implant, and the intrauterine LNG system (Levonova® or Mirena®).

Levonorgestrel primarily acts through thickening the cervical mucus; thus, it will obstruct the sperm penetration into the uterus.[1,2] Besides, it also inhibits ovulation in over 50% of the menstrual cycles[3,4] and has a suppressive effect on the endometrium to reduce the likelihood of nidation.[5] Both mechanism of action above provide protection against pregnancy efficiently.

The beneficial features of Norplant® include long contraceptive activity, high contraceptive efficacy, absence of estrogen side effects, and convenience due to no daily attention needed. Furthermore, it is completely reversible and the side-effects are mainly mild and transient. Norplant® capsules have been studied extensively for clinical efficacy and safety by independent clinicians and agencies throughout the world for many years. However, insertion and removal of the implant needs sufficient training.

On the other hand, Jadena® is developed as two implantable rods in order to make insertion and removal of the contraceptive device easier. Both the release rate of LNG from Jadena® rods and plasma hormone concentrations achieved are comparable to those of the Norplant® capsules.[6,7] The two preparations are similar in terms of contraceptive efficacy for three years and the occurrence of side effects.[8-10]

Jadena® is a subdermal tube implant containing 75 mg of LNG each, whereas Norplant® is a subdermal capsule containing 36 mg LNG each. Jadena® implant consists of two rods sizing nine millimeters longer than the Norplant® capsules. The period of Jadena® rod user is for three years; meanwhile, the Norplant® capsules provide longer period for five years of effective contraceptive protection.

Norplant® was introduced into the Family Planning Program (FPP) in Indonesia since 1981. It becomes popular among Indonesian community.[9] By March 1997, there were 2.4 million women using Norplant® as their contraceptive method in Indonesia. This represents about three quarters of Norplant® users all over the world. Recently, Jadena® was also registered in Indonesia and it had already been used by about 2,000 Indonesian women. However, data comparing the efficacy and acceptability of Norplant® and Jadena® are still not available in Indonesia. Therefore, this study aims to provide a randomized comparison between Jadena® and Norplant® in terms of efficacy and acceptability among Indonesian women.

METHODS

This study was a phase IV, open label, randomized, and multicenter studies throughout Indonesia. Subjects were recruited from 6 large cities in Indonesia, namely Medan (Universitas Sumatera Utara), Palembang (Universitas Sriwijaya), Jakarta (Universitas Indonesia), Semarang (Universitas Diponegoro), Surabaya (Universitas Airlangga) and Makassar (Universitas Hasanuddin) between August 1998 and February 1999.

Subjects were Indonesian adult women having been randomized to receive Jadena® or Norplant® as their contraceptive method. The sample size was determined through formula proposed by Pocock. To demonstrate a ten-fold increase in cumulative 3-year pregnancy rate (0.5 per 100 women-years), the minimum sample size was 272 subjects per treatment group.

A total of 600 women were needed which meant 100 women recruited from each center. This study was the first design to be followed-up for three years; however, another 2 years were added to complete 5-year observation and follow-up. Subjects were followed every year in 12 visits, such as at month-1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. We recruited 18-40-year old women, not currently pregnant, be regularly exposed to the risk of pregnancy, without exposure to injectable steroid in the predicting 6 months, be willing to rely solely on the implant randomly assigned for her contraceptive method, be willing to return the clinic for regular follow-up. All the participants were informed of the purpose, risk, and benefits of the study and they had to sign the written informed consent.

Subjects were excluded from the study if there was any kind of cancers, undiagnosed abnormal uterine bleeding (AUB); thromboembolism or severe cardiovascular problem; mental illness, depression or epilepsy; severe and frequent headaches; diabetes mellitus; active liver disease or jaundice; regular treatment with enzyme-inducing drugs, such as barbiturates, phenytoin, carbamazepine or rifampicin; blood pressure greater than 160 mmHg systolic or 100 mmHg diastolic; bloody breast discharge; severe hirsutism; pregnancy or suspected pregnancy; current evidence of pelvic

inflammatory disease; and participation in another clinical study on the previous three months.

Study Endpoints

The primary efficacy variable was the pregnancy rate calculated using the Kaplan-Meier product limit method. Secondary efficacy parameters were the alteration in menstrual cycles, discontinuation or continuation rates, rates of implant removal due to menstrual problems and/or medical reasons, and the duration of implant insertion and removal from asepsis to wound closure. All data were based on the information reported by the women using Jadena® or Norplant®. We also investigated several safety parameters including laboratory parameters, general state of health, adverse events, concomitant medications, body weight, and vital signs.

Data Management and Analyses

All variables were described according to their types using univariate statistics (mean and standard deviation for continuous data, frequency and percentage for categorical data). The primary efficacy variable in this trial was the pregnancy rate estimated using the Kaplan-Meir product limit method. The two treatment groups were compared using the Wilcoxon rank-sum test. A significance level (α-level) of 0.05 was used for all statistical tests. Secondary and safety variables were presented descriptively.

RESULTS

There were 600 women enrolled in this study. They were randomized to receive Jadena® (301 women) or Norplant® (299 women). Their mean age was 29.8 (SD 5.3) years old, ranging from 18 to 40 years old. Subjects using Norplant® were older than subjects using Jadena® (p=0.008). On the average; however, the women from both implant groups were relatively similar to the demographic characteristics, such as body weight, body mass index (BMI), and blood pressure (Table 1). All subjects had normal body weight and BMI. All subjects had been pregnant and/or had delivered at least once. The mean number of previous pregnancies were 2.8 (SD 1.5). The mean number of live birth were 2.6 (SD 1.4). Higher parity was observed in women on Jadena® than Norplant® (p=0.04). At baseline, most women (87.6%) reported normal or usual menstrual pattern. Five-point four percent of these women had amenorrhea. Almost one-third (32.5%) of the subjects wanted more children. The most popular (49.8%) contraceptive method used prior to the study enrollment was the combination of oral contraceptive and majority of them (38.7%) had their last contraceptive used less than 31 days before. More than half of the women (60.3%) did not practice breastfeeding. Almost all subjects (95%) reported vaginal delivery at the last pregnancy. Cytological examination data were available in 591 subjects. The results were mostly classified into CI (75.1%), while CII was found in 24.2% of women. None was classified as CIII.

Efficacy Assessment

Primary end point

No pregnancy was observed in both contraceptive users. However, an intrauterine pregnancy was found in Norplant® group which had been confirmed that it started before her enrollment into the study. The implant was removed immediately and she delivered a baby spontaneously at term gestational age. The Kaplan-Meier product limit method showed that non-pregnancy probabilities were not different between the two implants (Table 2). Therefore, both contraceptive methods showed similar efficacy in controlling pregnancy over 5 years.

Secondary endpoints

The prevalence of dysmenorrhea was considered low. The prevalence was not significantly different between baseline and after 5 years both in women using Jadena® (2.0% vs. 2.5%; p=0.812) and Norplant® (2.4% vs. 2.0%; p=0.977). The menstrual changes occurred in majority of subjects in the first two years. Improvement of menstrual irregularities increased after three years. The pattern of menstrual changes was similar between Jadena® and Norplant® users (Figure 1).

Discontinuation or continuation rates

At the end of the third year and after obtaining written consent to extend the observation period by an additional 2-year, 411 of the 600 women (68.5%) agreed to continue the study; consisting of 210 women using Norplant® (70.2%) and 201

women using Jadena® (66.8%). Continuation rates per year were shown on Table 3. The difference in discontinuation rates between the two contraceptive methods from year-1 to year-5 was not significantly different (p=0.746).

Rates of implant removal due to menstrual problems and/or medical reasons

Premature removal of the implant was decided by 154 out of 217 women. The reason mostly was because of the desire to get pregnant (19.4%). Others had menstrual problems, such as metrorrhagia (4.1%), amenorrhea (3.2%), spotting (2.3%), prolonged menstrual flow (1.8%), and heavy menstrual flow (1.4%). The details on the primary reasons for implant removal in both groups were given on Table 4.

Duration of the implant placement and removal

Nearly all subjects (99.2%) had their implant placed on their left upper arm. There were neither reported complications nor difficulties encountered during implant placement. From aseptic to skin closure, the surgical procedure took an average of 3.1 (SD 1.5) minutes, varied from as short as 1 minute to as long as 10 minutes. The procedure for Jadena® placement was shorter than NorplantS® (2.2 (SD 0.9) vs. 4.1 (SD 1.3) minutes; p<0.001).

The surgical procedure for implant removal took an average of 8.7 (SD 4.9) minutes. Procedures for Jadena® removal was significantly shorter than Norplant® removal (6.4 (SD 4.1) vs. 10.5 (SD 4.7) minutes; p<0.001). Most subjects (89.5%) did not feel any complication during the procedure.

Safety Assessment

During the 5-year period, 37 (6.2%) of subjects experienced at least one adverse event (AE), comprising 20 (6.6%) women on Jadena® and 17 (5.9%) women on Norplant®. Most AEs (64.9%) was mild; however, 6 women (16.2%) experienced moderate AEs, which all belonged to Jadena® group. Two patients had severe AEs; one on Norplant® was diagnosed with severe hypertension during visit-11 and the another one on Jadena® experienced severe cramping on the arm at visit-11 which requested to be removed. One woman on Jadena® died due to dengue hemorrhagic fever (DHF) and it was not related to the contraceptive method.

Adverse events reported by women using Jadena® included spotting (5 women), bleeding (3 women), influenza (2 women), dizziness (2 women), expulsion (1 woman), cardiomegaly (1 woman), cramp at the implant site (1 woman), death due to DHF (1 woman), headache (1 woman), local infection (1 woman), menometrorrhagia (1 woman), metrorhagia (1 woman), and numbness (1 woman). In women using Norplant®, the adverse events were headache (5 women), spotting (3 women), hypertension (2 women), influenza (2 women), local infection (2 women), abscess (1 woman), bleeding (1 woman), dizziness (1 woman), emesis gravidarum (1 woman), irregular bleeding (1 woman), numbness (1 woman), palpitation (1 woman), pelvic pain/dyspareunia (1 woman), and sweating (1 woman).

DISCUSSION

In the beginning, this study was designed for 3 years, but it was extended for another 2-year to complete a 5-year observation of both implant system. The first study on extended use (5 years) of the two-rod implants (Norplant II®) was conducted in China, with a failure rate of 0.65 per 100 users and continuation rate of 65.3 per 100 users. These rates were similar to that of the capsule implant users.[8] Continuation of two-rod LNG implants has also been tried in US study when the 3-year cumulative pregnancy rate was 0.8 per 100.[10] For a 5-year period, the 2-rod LNG implants were equivalent to the 6-capsule LNG implants regarding to safety and efficacy parameters. It offers the advantage to insert more easily and remove more rapidly.[10] The cumulative 5-year pregnancy rate of LNG implants was comparable to that of tubal ligation.[11]

Our study subjects were older (29.8 years old) than the US study, which had the mean age at baseline of 25.5 years old.[10] This could be because all subjects in our study was married women who had given delivering at least once. It also reflects that contraceptive use is uncommon in young, unmarried women adults in Indonesia. Other characteristics in this study were the subjects' body weight and BMI, which showed the normal range. On the contrary, subjects in the US study showed much higher body weight with a mean of 62.4 kg at baseline.[10] Weight gain is an important problem

during implant use; thus, it should be considered since the beginning.

The primary reason for discontinuation after three years of use was the subjects' plan for pregnancy. However, a substantial number of subjects (more than 70%) also experienced menstrual problems. Menstrual irregularities (lighter or heavier menstrual flow and amenorrhea) were occurred in most subjects at the first year of use. Although menstrual change was common, most subjects decided to continue the implants. The overall level of satisfaction was high and even the continuation rates at the end of the first year were better than combined oral contraception.[12] Menstrual change was also reported as the common AE during the first year of Norplant® use in Singapore. However, these menstrual irregularities appeared to be reduced as the time and they were tolerated since 97% of the women continued at the end of the first year.[13] Study on bleeding patterns on 234 Norplant® users for 5 years showed that a substantial number of subjects (66.3%) had irregular cycles during the first year and 7.1% were amenorrhea. However, by the fifth year of use, only 37.5% subjects had irregular cycles and none had amenorrhea. Thus, the menstrual irregularity improved after the first year of use.[14]

In a minority of subjects, prolonged bleeding/spotting (8.2%) and irregular bleeding (5.6%) were the primary reasons for removal.[10] A study among Norplant® users in Europe found that discontinuation before 5 years of implant was related mostly to irregular bleeding.[15] Risk factors for Norplant® discontinuation for perceived menstrual problems were higher education level (more than 12 years), had used no contraceptive in the preceding month before Norplant® insertion, or had a relatively long duration of menstrual flow at admission.[16] Discontinuation rate due to menstrual problems increased from 9.4 per 100 women at the end of year-2 to 16.4 per 100 women at the end of year-5.[16]

In a phase III clinical trial, the 2-rod subdermal implants showed high continuation rates, such as 88.1% at 1 year of use and 73.5% after 2 years. The main reason for discontinuation was menstrual disturbance, mainly prolonged bleeding.[17] Menstrual irregularity with the 2-rod system was not significantly different from that observed with Norplant®. Normal menstrual bleeding was uncommon during the first three months of use, but the prevalence increased to almost 70% at the end of five years. Amenorrhea was uncommon after two years of use.[18]

Removal due to headache (4.7%) and weight gain (4.0%) were the next most frequent medical reasons after menstrual problem in US study.[10] In our study, only three subjects asked the implants remove for headache and one subject for having weight gain. Increased body weight of 1 kg per year on average was observed in implant users.[11] Higher body weight gain of 2.9 kg was observed in intrauterine LNG device at 12 months.[19]

Other rare adverse effects that might be a medical concern were local infection and hypertension. Local infection was rare (0.4 per 100 users at 24 months) in the phase III clinical trial of 2-rod implant.[17] A study among 2,674 Norplant® acceptors from 7 countries and followed for one year showed that the incidence rate of infection was low (0.8%). Insertion site infection and implant expulsion were reported after the first two months of use.[20] A study on 267 Norplant® users showed that neither systolic nor diastolic blood pressures were affected. Increasing blood pressure was more likely to be associated with the women's age, obesity and family history of hypertension.[21]

In this study, Jadena® use was associated with significant shorter time of insertion and removal. In a 3-year randomized, controlled study, implant removal of the 2-rod system took about half the time required for 6-capsule implants ($p<0.001$).[22] Difficult implants removal might be occurred in about 3% subjects due to deeply placed or poorly aligned implant or severe reaction to local anesthetic agent.[11] Implant removal was more difficult than insertion because in step of time, fat and fibrous tissue could develop around the capsules. Delayed removal of implant could be seen in many Norplant® users in Indonesia. A large study involving 2,979 Indonesian women using Norplant® in 14 provinces showed that 66% of the women had implant removal by the end of the fifth year (90% by sixth year).[23] Therefore, the 2-rod implant system which was easier to insert could potentially reduce the difficulties during implant removal after a long period of use.

Cervical cytology might be a concern among women who used long-term hormonal contraception. However, subdermal LNG implant has been proved to be safe during five years of use.[24] In this study, there was no abnormal cytology or cervical

Table 1. The Characteristics of the Study Subjects (n=600)

	Jadena® (n=301)	**Norplant® (n=299)**
Age, years (mean (SD))	28.8 (1.3)	30.0 (1.7)
Body weight, kg (mean (SD))	50.7 (2.3)	50.9 (2.1)
Body mass index, kg/m2 (mean (SD))	21.9 (0.6)	22.1 (0.6)
Systolic blood pressure, mmHg (mean (SD))	112.9 (0.9)	113.4 (2.0)
Diastolic blood pressure, mmHg (mean (SD))	73.8 (1.9)	73.6 (2.3)
Number of previous pregnancies (mean (SD))	2.7 (0.4)	2.9 (0.4)
Parity (mean (SD))	2.5 (0.4)	2.7 (0.3)

SD=standard deviation

Table 2. Kaplan-Meier Estimates for non-Pregnancy Probabilities*

	Jadena® (n=301)		**Norplant® (n=299)**	
	Probability	SD	Probability	SD
Year 1	0.920	0.016	0.916	0.084
Year 2	0.890	0.018	0.886	0.018
Year 3	0.664	0.027	0.702	0.026
Year 4	0.651	0.027	0.692	0.027
Year 5	0.000	0.000	0.000	0.000
Median time	60 months		60 months	

**Not significant at alpha 0.05; SD=standard deviation*

Table 3. Continuation Rates of using Levonorgestrel Contraceptive Implant

	Year 1		**Year 2**		**Year 3**		**Year 4**		**Year 5**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Jadena® (n=301)	287	95.3	274	91.1	201	66.8	199	66.1	185	61.5
Norplant® (n=299)	282	94.3	273	91.3	210	70.2	208	69.6	198	66.2

Table 4. Primary Reasons for Discontinuation (Implant Removal) after Three Years*

Primary reason	**Jadena®**	**Norplant®**	**Total**
No reason indicated	25	32	57
Intrauterine pregnancy	0	1	1
Menstrual problems			
Frequent irregular bleeding	4	4	8
Heavy menstrual flow	2	1	3
Prolonged menstrual flow	1	2	3
Amenorrhea	3	4	7
Spotting	4	1	5
Placement problems			
Infection at site	1	4	5
Expulsion of 1 or more implants	1	2	3

Primary reason	Jadena®	Norplant®	Total
Cardiovascular			
Hypertension	0	1	1
Not specified	2	0	2
Other medical problems			
Headache	1	2	3
Pain at the implant site	1	0	1
Weight change	1	0	1
Personal			
Planning of pregnancy	24	12	36
Widowed/divorced/separated	2	1	3
Moving	6	6	12
Other personal reasons			
Subject objection	3	6	9
Husband objection	1	2	3
Death of the husband	1	0	1
Not specified	10	5	15
Other removal problems	0	1	1

**multiple response*

change to lead to premature removal or discontinuation of both implant systems.

CONCLUSION

The new 2-rod LNG subdermal system (Jadena®) showed similar efficacy with the old 6-capsule LNG subdermal system (Norplant®) in term of birth control. Both implants system also have similar tolerability profile. Jadena® is easier to insert and remove than Norplant®.

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Research Article

The Outcome on Conservative Surgical Treatment of Adenomyosis

Luaran Operasi Konservatif bagi Penderita Adenomiosis

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Abstract

Objective: To understand the outcome on conservative surgical treatment of adenomyosis.

Methods: A retrospective cohort study followed for 2 years from 2010 to 2012 of women with adenomyosis were diagnosed by transvaginal sonography and confirmed histologically. Subjects divided into women who were treated by adenomyosis resection (with/without Osada's technique) and who were underwent hysterectomy.

Results: After the surgery, as many as 40 patients (81.63%) did not feel any pain (VAS 0), and 9 patients (18.37%) still felt pain. For the fertility outcome, we had 8 patients (20.51%) getting pregnant naturally without any fertility intervention. Two patients (5.13%) had successfully conceived by IVF. According to the type of surgery, from 8 natural pregnancy, 7 patients (87.50%) was underwent conventional resection of adenomyosis and 1 patients (12.50%) underwent Osada's procedures. Two patients who were conceived by IVF, both of them were underwent Osada's resection.

Conclusion: Adenomyosis resection both conservative or Osada's procedures actually has a better outcome for relieving pain; therefore, some patients can still have a child.

[Indones J Obstet Gynecol 2016; 4-4: 198-202]

Keywords: adenomyosis resection, conventional resection, infertility, Osada's procedure

Abstrak

***Tujuan**: Untuk mengetahui keberhasilan operasi secara konservatif bagi penderita adenomiosis.*

***Metode**: Penelitian ini menggunakan studi restropektif yang diikuti selama 2 tahun mulai tahun 2010-2012 pada pasien adenomiosis yang diagnosis berdasarkan pemeriksaan sonografi transvaginal dan dibuktikan secara histologi. Subjek dibagi menjadi dua kelompok, yaitu yang ditangani dengan reseksi adenomiosis (dengan/tanpa teknik Osada) dan yang ditangani dengan histerektomi.*

***Hasil**: Setelah dilakukan operasi, 40 pasien (81,63%) tidak lagi merasakan nyeri (VAS 0), dan 9 pasien (18,37%) masih merasakan nyeri. Untuk keberhasilan kehamilan, 8 pasien (20,51%) hamil secara alami tanpa intervensi kesuburan apa pun, dan 2 pasien (5,13%) berhasil hamil dengan teknik fertilisasi in vitro (FIV). Berdasarkan tipe operasi adenomiosis, dari 8 kehamilan alami, 7 pasien (87,50%) dilakukan dengan reseksi adenomiosis secara konservatif dan 1 pasien (12,50%) dengan Osada. Dua pasien yang berhasil hamil dengan FIV, reseksi adenomiosis dilakukan dengan teknik Osada.*

***Kesimpulan**: Reseksi adenomiosis, baik konservatif maupun Osada memiliki keberhasilan yang baik dalam menghilangkan keluhan nyeri dan beberapa pasien dapat tetap memiliki anak.*

[Maj Obstet Ginekol Indones 2016; 4-4: 198-202]

***Kata kunci**: infertilitas, reseksi adenomiosis, reseksi konvensional, prosedur Osada*

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INTRODUCTION

Bird et al. defines adenomyosis as the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands, and stroma surrounded by the hypertrophic and hyperplastic myometrium.[1,2] The disease has been recognized since the end of the 19th century, but during the first quarter of the 20th century, all mucosal invasions in the peritoneal cavity or within the uterine walls were labeled as 'adenomyomas'.[3]

The incidence of this disease usually occurs to women at perimenopause period; however, nowadays, many women at reproductive age suffers from adenomyosis. Some studies said this condition was due to the changes of lifestyle.[2]

The symptoms are various, including dysmenorrhea (80%) as the most frequent symptom presented by the patients. Other symptoms are pelvic pain (50%), infertility (40%), and menstrual disturbance (20%). Apart from that, there are less often complaints such as menorrhagia, dyspareunia, suprapubic pain, uterus enlargement, and some women do not have any complaints.[4,5]

The effective treatment requires more radical resection of the affected tissues. It is still controversial between the radical procedure with hyster-

ectomy and conservative surgery by adenomyosis resection.[3,6,7] Since 1952, surgery for adenomyosis performed with resection of adenomyosis, followed by the reconstruction of the uterus wall (called by conservative surgery). In 2010, Hisao Osada had introduced surgical technique initiated by placing a temporary tourniquet around the lower uterine segment of the uterus to prevent the massive bleeding. The operator would open the uterus boldly all the way down to the endometrial lining. The non-demarcated adenomyotic tissue was excised leaving a centimeter on the endometrial side and a centimeter on the serosal (outer) side of the uterus. Furthermore, the remaining muscle of this debulked adenomyotic uterus musculature would be closed with many layers of sutures, all non-overlapping flaps, to prevent the risk of rupture.[7] Therefore, this study aims to understand the outcome on conservative surgical treatment of adenomyosis.

METHODS

This retrospective cohort study was performed at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. All medical records of patients with a diagnosis of adenomyosis between January 2010 and November 2012 were reviewed. All patients already underwent laparotomy adenomyosis resection with or without GnRH agonist as adjuvant treatment.

We collected 96 patients diagnosed adenomyosis. They had already done surgery treatment; whereas, 49 patients underwent adenomyosis resection and the remaining of 47 patients underwent hysterectomy.

Diagnosis of adenomyosis was confirmed with transvaginal sonography and histological evaluation after surgery. About 18 women undertook adenomyosis resection by Osada's procedure. Meanwhile, 31 women carried out conventional adenomyosis resection. All surgery procedures were well documented on medical records.

Informed consent was obtained and approved by The Ethical Committee, Faculty of Medicine Universitas Indonesia.

RESULTS

Of 96 patients who diagnosed adenomyosis between January 2010 and November 2012, 47 patients (48.96%) ran into hysterectomy. Almost all patients diagnosed with adenomyosis, presented severe dysmenorrhea (having Visual Analog Scale/ VAS >7) and some patients said about dyspareunia. Thirty-three patients caused by primary infertility went through adenomyosis resection. On the other hands, all patients performed hysterectomy already had married, the average age was 45.52 (SD 3.61) years old, 37 patients already had at least 1 child, and 1 patient experienced primary infertility for 10 years; but, she already agreed to have hysterectomy. Age of patients undergoing either hysterectomy or adenomyosis resection was ranged between 28 and 49 years old, which all of them still had regular menstrual period.

Among 49 patients carrying out adenomyosis resection, 31 of them (32.29%) were held conventional adenomyosis resection and the mean age of them was 35.83 (SD 3.51) years old. Eighteen patients (18.75%) underwent surgery by Osada's procedure with mean age were 33.63 (SD 3.48) years old.

Table 1. Mean Age of Subjects based on Surgery Method

Surgery Method		n (%)	Age (Mean (SD))
Hysterectomy		47 (48.96)	45.52 (3.61)
Resection	Conventional	31 (32.29)	35.83 (3.51)
	Osada	18 (18.75)	33.63 (3.48)

Looking at the symptoms, dysmenorrhea was the most common complaints (69.39%) of patients to seek treatment in hospital. While, other symptoms such as pelvic pain, dyspareunia, and bleeding became less common. Regarding to the fertility problem, 33 patients (67.35%) came with primary infertility, 6 patients (12.24%) with secondary infertility, and 10 patients (20.41%) with no fertility problem.

Before surgery, most patients presented with dysmenorrhea with the VAS of 7-10. One year after surgery, 40 patients (81.63%) did not feel pain (VAS 0) and there were no patients complaining with persistent pain. Besides, 9 patients (18.37%) were still perceived less pain without further treatment.

Table 2. Clinical Characteristics and Symptoms after Surgery

Variables		n (%)
Parity	0	37 (75.51)
	1	6 (12.24)
	2	4 (8.16)
	3	2 (4.08)
Symptoms	Dysmenorrhea	34 (69.39)
	Pelvic pain	7 (14.29)
	Dysmenorrhea and dyspareunia	4 (8.16)
	Dysmenorrhea and pelvic pain	3 (6.12)
	Hemorrhage	1 (2.04)
Fertility	Primary infertility	33 (67.35)
	Secondary infertility	6 (12.24)
	No infertility	10 (20.41)
Symptoms after operation	No symptom	40 (81.63)
	Persistent symptoms (persistent VAS)	0 (0.00)
	Decreased symptoms (VAS<2)	9 (18.37)

The duration of infertility was 4.94 (SD 3.52) years for primary infertility and 7.33 (4.68) years for secondary infertility. Concerning to the result of fertility, there were 8 patients (20.51%) conceived naturally without fertility intervention, 2 patients were successfully delivered by cesarean section (CS), and no events of uterine rupture. Until finishing this study, four patients were still continuing their pregnancy and having more than 20 weeks of gestational age. Unfortunately, the 2 patients who conceived naturally experienced miscarriage at 3 months of pregnancy. Two patients (5.13%), which had been successfully prepared by in vitro fertilization (IVF), was delivered by CS. According to the surgery method, 8 women who succeeded natural pregnancy, 7 patients (87.5%) were performed conventional adenomyosis resection and 1 patient (12.5%) was underwent the Osada's procedure resection. Two patients who were conceived by IVF, both of them were resected though Osada's procedure.

DISCUSSION

Adenomyosis may be described as a diffuse invasion of endometrial element into the uterine myometrium. Adenomyosis differs from fibromyomatous growth; whereas, there is no discrete borders between the normal uterine tissue and the lesion. Therefore, a clear dissection plane is difficult to establish so that this procedure is challenging.[3,7]

In addition to infertility, high grade of adenomyosis also causes severe dysmenorrhoea and hypermenorrhoea, which adversely affects the woman's well-being. The management for the latter two symptoms includes long-term hormonal therapy, analgesics, and finally hysterectomy. For those who wish to preserve reproductive function, the surgical management of severe adenomyosis cases is particularly difficult because the operator has to excise diffusely involving tissue and prevent the occurrence of uterine rupture in the event of pregnancy.[3,4,8]

Table 3. Fertility Outcome based on Surgery Method

Pregnancy	n (%)	Osada Procedure (%)	Conventional resection (%)
Natural pregnancy	8 (20.51)	1 (12.50)	7 (87.50)
Pregnancy with IVF	2 (5.13)	2 (100.00)	0 (0.00)
Unpregnant	29 (74.36)		

The requirement of adenomyosis surgery for the purpose of preserving reproductive functions is as follows. Firstly, it is ideal if tubal patency can be retained to allow for natural pregnancy. Secondly, the uterine cavity must be retained intact in order to assure implantation. Thirdly, the uterine wall must be properly reconstructed to enable it to sustain fetal growth following conception. In other words, the operator must reconstruct the uterine wall which can endure the thin lines associated with the expansion of the uterine cavity. In the end, it results the development of pregnancy.[7,9,10]

There is also the problem on recurrence of the disease. In this case, we had to observe the patient routinely and perform ultrasound examination to investigate whether there was a new mass. Unfortunately, this was not a routine procedure in our hospital. Up to a year follow-up, all patients who carried out resection did not complain about severe dysmenorrhea.[5]

Some patients (9 patients) still presented pain on the low VAS score so that they did not obtain the analgesic medication. Among 49 patients undergoing surgery, 22 of them were given GnRH agonist (Tapros®), 10 patients did not receive any treatment; however, we did not have any information about other 17 patients. Both group of patients who were given GnRH agonist or not had no different outcome on the pain score measured by VAS after surgery.[11]

Based on the observation on two methods of adenomyosis resection, the first was adenomyosis conventional resection (performed for 31 patients (32.29%)) compared to Osada procedure (performed for 18 patients (18.75%)). We did not find any significantly different outcome between these surgical techniques. Close observation shoud perform for many years into the future to conclude the final outcome between these two procedures. Studies that had been conducted by Osada in 2011, the ten-year observation after Osada procedure which included 104 subjects showed excellent results in the likelihood of adenomyosis recurrence.[3,6,7]

Regarding to the result of fertility, among 49 patients, 33 of them (67.35%) came with primary infertility, 6 patients (12.24%) had secondary infertility problem. After resection performed, 8 patients (20.51%) had a natural pregnancy with 2 of them underwent a caesarean delivery and their babies were in good condition. Two patients (5.13%) who conceived with IVF procedure and underwent cesarean section delivery. Among these two patients who became pregnant by natural conception; unfortunately, they had miscarriage at 3 months of pregnancy. This is in accordance with study by Lukes, et al., which stated that the risk of miscarriage in adenomyosis was four times higher than women without adenomyosis.[9,12]

The low percentage of pregnancy after surgery was due to several reasons. Possible causes were firstly, postoperatively, almost all patients did not come back to the follow up on their fertility problem. Secondly, fertility work-up was not performed completely before the surgery because most of the main complaints of patients coming to the hospital was severe pain. Among 7 patients having successful pregnancy (more than 20 weeks of gestational age), only 2 patients with IVF pregnancy came for antenatal care at our hospital.

CONCLUSION

Adenomyosis resection offers new hope to patients who want to preserve their uterus for several reasons. Adenomyosis resection, either conventional or Osada's procedure actually has better outcomes for pain relief and similar result for the heredity. Fertility work-up (both husband and wife) and some reproductive interventions, such as intrauterine insemination (IUI) or IVF may increase the probability of pregnancy for women who suffer from adenomyosis.

ACKNOWLEDGEMENTS

The author would like to express our gratitude to medical record staffs and to dr. Liva Wijaya, dr. Johnny Judio, and dr. Matthew M for their assistance in preparing this manuscript.

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Research Article

Anti-Müllerian Hormone Level in Laparoscopic Cystectomy

Kadar Anti Müllerian Hormon pada Laparoskopi Kistektomi

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Abstract

Objective: To evaluate the impact of laparoscopic cystectomy using cautery and suturing technique on the ovarian reserve represented by the level of Anti-Müllerian Hormone (AMH) serum.

Method: This used prospective cohort study design conducted in Dr. Wahidin Sudirohusodo Hospital, Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Hasanuddin, Makassar, from November 2014 to October 2015. We got total samples of 60 subjects divided into cautery and suturing group. Anti-Mullerian hormone serum test was examined on all subjects pre and post laparoscopic cystectomy.

Result: The result indicated a significant decrease of AMH level undergoing laparoscopic cystectomy both cautery and suturing technique; whereas, more dominant results were showed in the cautery group ($p<0.05$). In the 95% confident interval (CI), the mean decrease of cautery group was 0.87 ng/ml and 0.31 ng/ml for suturing group. Both groups showed greater decrease in bilateral cyst, endometriotic type of cyst, and the cyst diameter of less than 5 cm; although these differences were not statictically significant ($p>0.05$).

Conclusion: The decline in the number of ovarian reserve as described by the reduction of AMH level occurs significantly in both cauterization and suturing technique, which are more dominant reduction in the cauterization group.

[Indones J Obstet Gynecol 2016; 4-4: 203-207]

Keywords: Anti-Müllerian Hormone, laparoscopic cystectomy, ovarian reserve

Abstrak

***Tujuan**: Mengevaluasi pengaruh laparoskopi kistektomi dengan teknik kauter dan penjahitan terhadap cadangan ovarium yang direpresentasikan oleh kadar serum hormon anti mullerian (AMH).*

***Metode**: Penelitian dengan rancangan kohort prospektif dilaksanakan di RS dr. Wahidin Sudirohusodo, Departemen Obstetri dan Ginekologi Fakultas Kedokteran Universitas Hasanudin (Unhas) di Makassar mulai November 2014 hingga Oktober 2015. Didapatkan sampel sebanyak 60 subjek yang memenuhi kriteria dan dimasukkan pada kelompok kauter dan penjahitan. Semua subjek dilakukan pemeriksaan AMH pre dan post laparoskopi kistektomi.*

***Hasil**: Penelitian menunjukkan penurunan yang bermakna dari kadar AMH pada sampel yang menjalani laparoskopi kistektomi dengan teknik kauter maupun penjahitan, dengan hasil yang lebih dominan pada kelompok kauter ($p<0,05$). Pada nilai interval kepercayaan (IK) 95% didapatkan rata-rata penurunan pada kelompok kauter dan penjahitan sebesar 0,87 ng/ml dan 0,31 ng/ml. Pada kedua kelompok didapatkan penurunan AMH yang lebih besar pada kista bilateral, tipe kista endometriosis, dan ukuran kista <5 cm, namun perbedaan antar kedua kelompok tidak bermakna secara statistik ($p>0,05$).*

***Kesimpulan**: Penurunan jumlah cadangan ovarium yang digambarkan oleh AMH terjadi secara signifikan pada kedua prosedur hemostasis dengan energi panas kauterisasi dan penjahitan, dengan penurunan lebih dominan pada kelompok kauterisasi.*

[Maj Obstet Ginekol Indones 2016; 4-4: 203-207]

***Kata kunci**: cadangan ovarium, hormon anti-mullerian, laparoskopi kistektomi*

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INTRODUCTION

Ovarian cyst is the most common form of mass on ovarium. The incidence of ovarian cyst was reported between 5 and 15 percent of all the gynecological tumor.[1]

The clinicians usually diagnose ovarian cyst through pelvic examination and ultrasound (USG) imaging modalities; then, they proceed with tumor marker assessment to detect the possibility of malignancy. After diagnosing, they manage the ovarian cyst through either conservative observation or surgery.[1]

Generally, two types of ovarian cyst usually found are functional cyst and endometriosis. Each type of cyst has its own unique characteristics so that the operator can destroy the ovaries differently during performing the laparotomy or laparoscopic cystectomy. In patients with ovarian cyst who undergo laparoscopic cystectomy, there will be normal ovarian tissue damaged during the surgical procedure, either due to sticky tissues or cauterization procedure. Normal ovarian tissue should be maintained as well as possible because it is related to the ovarian ability to maintain the ovulation.[2]

Anti-Müllerian Hormone (AMH) is hormone produced by the granulosa cells of primary ovarian follicles. The highest expression is during preantral and antral follicles phase, and it will no longer be detectable when the follicles undergo atresia. Anti-Müllerian Hormone serum level is strongly associated with the number of antral follicles, which describe the number of remaining primordial follicles reserve. The reserve of primordial follicles can be used as an illustration of the ovulation induction success.[3] The more severe of damage to ovarian tissue after cauterization process during laparoscopic cystectomy, the less number of normal follicles left; therefore, AMH level will decline after surgery.[4] During laparoscopic cystectomy procedure, there is a chance for the damage of normal ovarian tissue because of heat cauterization. As a result of this procedure, the patients have an iatrogenic decline in the number of ovarian follicles causing premature menopause. Apart from that, AMH is used as a prognostic factor for induction of ovulation in in-vitro fertilization; whereas, it needs sufficient number of ripe ovarian follicles.[5]

Over the last twenty years, AMH, Follicle Stimulating Hormone (FSH), Estradiol (E_2), and inhibin B serum level have been studied to describe the number of ovarian cells reserve. However, FSH, E_2, and inhibin B serum markers are associated with negative feedback on the pituitary-ovarian axis, so that the level of them will be fluctuated during menstrual phase. Meanwhile, the AMH serum level is relatively stable during the cycle. In conclusion, the AMH serum can be used as the reliable marker for ovarian follicle reserve compared with other markers.[2]

This study is conducted on women sufferring from ovarian cyst who had undergone laparoscopic cystectomy with intraoperative cauterization procedure. We compared between the pure suturing and without cauteterization technique. The AMH level serum on each patient was measured before surgery and continued by after surgery. The aim of this study is to determine the significant reduction on the AMH level in both sample groups with different techniques.

METHODS

This study was held in Dr. Wahidin Sudirohusodo as a teaching hospital with laparoscopic surgery facility, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin, Makassar, South Sulawesi. This study used a prospective cohort study design from November 2014 to October 2015. We obtained 60 women suffering from ovarian cyst who had undergone laparoscopic cystectomy procedure.

We examined AMH serum level thorugh blood. The blood samples were taken from each patient at the ventral region of the cubital cavity before and one month after the laparoscopic cystectomy procedure. We analyzed using paired t-test for the AMH serum level to compare the reduction quantity between cauterization and suturing group. We considered statitistically significant if p value less than 0.05.

RESULTS

We collected 60 samples fulfilling the inclusion criteria. They consisted of 30 samples who underwent intraoperative cauterization and the remaining 30 samples performing intraoperative suturing. The characteristics of subjects include age, educational level, marital status, parity, cyst location, type, size, and adhesion (table 1).

Table 1 showed that subjects who had undergone cauterization technique generally were 20-40 years old (90%), most of them graduated from senior high school (43%), had married (83.3%), and ever delivered more than or equal to 2 times (36%). The type of cyst was generally endometriosis (73.3%), located unilaterally (73.3%) with size of 5-10 cm (60%), and the cyst did not show adhesion (70%). Meanwhile, subjects doing the suturing techniques were 20-40 years (93.3%), educational level of senior high school (56.7%), had married (83.3%) with 1 parity (44%). Most of cyst typewas endometriosis (63.3%), located unilaterally (70.0%), with size less than 5 cm (66.7%), and no adhesion (66.7%). The statistical result using Shapiro-wilk normality test, we obtained p value more than 0.05; therefore, there were no statistically significant differences in age, educational level, marital status, parity, cyst location, type, size, and adhesion between cauterization and suturing group. Thus, both groups described fairly homogenous.

Table 1. Characteristics of Subjects

Characteristics	Technique		Total	p
	Cauterization	Suturing		
Age group (years old)				
20-40	27 (90.0)	28 (93.3)	55 (91.7)	1.000
> 40	3 (10.0)	2 (6.7)	5 (8.3)	
Education				
Junior high school	5 (16.7)	5 (16.7)	10 (16.7)	
Senior high school	13 (43.3)	17 (56.7)	30 (50.0)	0.513
University	12 (40.0)	8 (26.7)	20 (33.3)	
Marital status				
Married	25 (83.3)	25 (83.3)	50 (83.3)	1.000
Unmarried	5 (16.7)	5 (16.7)	10 (16.7)	
Parity				
0	8 (32.0)	5 (20.0)	13 (26.0)	
1	8 (32.0)	11 (44.0)	19 (38.0)	0.558
≥ 2	9 (36.0)	9 (36.0)	18 (36.0)	
Cyst location				
Unilateral	22 (73.3)	21 (70.0)	43 (71.7)	0.774
Bilateral	8 (26.7)	9 (30.0)	17 (28.3)	
Cyst type				
Endometriosis	22 (73.3)	19 (63.3)	41 (68.3)	0.405
Simple	8 (26.7)	11 (36.7)	19 (31.7)	
Cyst size				
<5 cm	12 (40.0)	20 (66.7)	32 (53.3)	0.195
5-10 cm	18 (60.0)	10 (33.3)	28 (46.7)	
Adhesion				
Present	9 (30.0)	10 (33.3)	19 (31.7)	1.000
Not present	21 (70.0)	20 (66.7)	41 (68.3)	

Table 2. The Difference of AMH Level Pre and Post Surgery According to Surgical Technique

Technique	Time	AHM Level (ng/ml)		p
		Mean	SD	
Cauterization	Pre surgery	3.56	3.10	0.011
	Post surgery	2.69	2.39	
Suturing	Pre surgery	4.27	2.60	0.028
	Post surgery	3.90	2.55	

In cauterization group, the average AMH level pre surgery was 3.56 ng/ml; whereas, it decreased to 2.69 ng/ml post surgery. In the suturing group, the average pre surgery AMH level was 4.27 ng/ml; while, the post surgery level was 3.9 ng/ml. Statistical result using paired t-test, we obtained p value of 0.011 in the cauterization group and 0.028 in the suturing group. It meant that there were statistically significant difference of the AMH level alteration either using cauterization or suturing techniques.

Table 3. Mean Changes of AMH Level According to Surgery Technique

Technique	AMH Level (ng/ml)		p
	Mean	SD	
Cauterization	0.87	0.98	0.005
Suturing	0.31	0.28	

The average alteration in AMH level on the cauterization technique was 0.87; while, the suturing technique was 0.31. Statistical result using independent t-test showed the p value of 0.005, it meant that there was significant difference in AMH level between two groups.

Table 4 explained that in unilateral cyst, the average decline of AMH level in the cauterization technique was 1.14 ng/ml and 1.00 ng/ml for suturing technique; whereas, for bilateral cyst, the average decline of AMH level in the cauterization technique was 1.25 ng/ml and 1.11 ng/ml in the suturing technique. Based on endometriosis cyst type, the average decline of AMH level in the cauterization technique was 1.23 ng/ml and 1.05 ng/ml in the suturing technique group. On the simple cyst type, the average change of AMH level in both cauterization and suturing techniques was 1.00 ng/ml each. Based on the presence intra-operative adhesion, the average decline of AMH level in the cauterization and suturing technique was 1.22 ng/ml and 1.10 ng/ml. Based on the cyst size group (<5cm), the AMH level in the cauterization and suturing technique dropped into 1.25 ng/ml and 1.00 ng/ml. In the group sized 5-10 cm, the AMH level in the cauterization technique declined 1.11 ng/ml and 1.10 ng/ml in suturing technique group. Independent t-test result pointed out p value more than 0.05 on cyst location, type, adhesion, and size. There were not significantly different in the reduction of AMH level between study groups.

DISCUSSION

This study showed that the average reduction of AMH level was greater in the cauterization group which was statistically significant ($p < 0.05$). We also found that the average AMH serum level dropped more largely on the sample with bilateral cyst (mean 1.25 ng/ml), endometriosis cyst (mean 1.23 ng/ml), presence of intraoperative adhesion (mean 1.22 ng/ml) and cysts sized <5 cm (mean 1.25 ng/ml); however, they were not statistically significant ($p > 0.05$). Another study by Celik, et al. also found that decreasing level of AMH was seen in bilateral, endometriosis cysts sized <5 cm. In small bilateral cyst, it was likely that the number of healthy ovarian tissue damaged or taken away would be a lot through observing the reduction of AMH level.[6]

Intraoperative cauterization procedure uses heat energy to burn tissues during hemostasis process. Heat from cauter can damage the surrounding healthy ovarian tissue and cause more primordial follicles damage. It is illustrated thorugh

Table 4. Difference of Homone Level According to Cyst Location, Adhesion, Size, and Type

Cyst	Cauterization		Suturing		p
	n	Mean (SD)	n	Mean (SD)	
Location					
Unilateral	22	1.14 (0.35)	21	1.00 (0.00)	0.083
Bilateral	8	1.25 (0.46)	9	1.11 (0.33)	0.485
Type					
Endometriosis	22	1.23 (0.43)	19	1.05 (0.23)	0.107
Simple	8	1.00 (0.00)	11	1.00 (0.00)	-
Adhesion					
Present	9	1.22 (0.44)	10	1.10 (0.32)	0.493
Not present	21	1.14 (0.36)	20	1.00 (0.00)	0.083
Size					
<5 cm	12	1.25 (0.45)	20	1.00 (0.00)	0.082
5 - 10 cm	18	1.11 (0.32)	10	1.11 (0.32)	0.931

the higher AMH level reduction.[7] In the suturing group, AMH reduction may occur because the operator accidentally drawed the ovarian parenchym during the excision of cyst wall. According to Roman, it generally happened because there was no clear barrier between cyst wall lining and ovarian cortex histologically. Therefore, it is estimated that the cyst wall excision can cause ovarian reserve reduction.[8]

Most of the ovarian cyst patients in this study were 20-40 years old. This was according to study by Tzadik which they stated that the peak incidence of ovarian cyst was on the reproductive aged women.[9] In terms of education, the majority of subjects was well educated. It was related to the ovarian cyst characteristic symptoms, namely asymptomatic for functional/simple cyst, or cyclic pain for endometriosis cyst. Patients with sufficient education will have good self-sensibility to feel the disorder and they will immediately check themselves despite of slight complaint.

The most common cyst found in this study was endometriosis cyst. This was in accordance with the highest incidence of endometriosis in reproductive aged women, both married and unmarried, where major symptoms complaint were dysmenorrhea, chronic pelvic pain, and infertility.[2]

Pre surgery AMH level obtained were varied. According to La Marca, AMH level was stable throughout the menstrual cycle compared with other ovarian reserve markers; although the result showed various among individuals. It occured because there was wide variability of the ovarian reserve in each individual. Currently, we still need further study in AMH level according to race, body mass index (BMI), and exposure to cigarette smoke.[10]

CONCLUSION AND RECOMMENDATION

The decline in the number of ovarian reserve as described by the reduction of AMH level occurs significantly in both cauterization and suturing technique, which are more dominant reduction in the cauterization group. This suggests that t cauterization using heat energy causes wide range of ovarian tissue damage. Further study should be conducted to evaluate other causes of Anti-Müllerian hormone level reduction other than iatrogenic factors, such as surgery.

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Research Article

Comparison of the Levator Hiatal Area

Perbandingan Area Hiatal Levator Ani

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Abstract

Objective: To determine the relationship of the levator hiatal area among nulliparous, primiparous, and multiparous women so that we can assess the prevalence of avulsion.

Method: A cross-sectional study design was used by evaluating the transperineal ultrasound results of all nulliparous, primiparous, and multiparous women in the Obstetrics and Gynecology Clinic of Dr. Cipto Mangunkusumo hospital from May to December 2015. We analyzed the data through SPSS using one way ANOVA to compare the levator hiatal dimension among the groups of women during Valsava maneuver and at rest.

Result: There were significant differences in levator hiatal area among nulliparous, primiparous, and multiparous women during Valsalva maneuver and at rest, which the mean (SD) was 22.26 (5.45) cm^2 (p=0.028) and 10.70 (2.26) cm^2 (p=0.012), respectively. Levator ani muscle avulsion was occurred in 1 out of 46 (2.2%) women from the primiparous and multiparous group.

Conclusion: There are significant differences in levator hiatal area during Valsalva and at rest among the groups.

[Indones J Obstet Gynecol 2016; 4-4: 208-211]

Keywords: avulsion, levator hiatal area, multiparous, nulliparous, primiparous

Abstrak

***Tujuan**: Untuk mengetahui hubungan area hiatal otot levator ani perempuan nulipara, primipara dan multipara saat istirahat/kontraksi dan manuver Valsalva serta mengetahui prevalensi kejadian avulsi.*

***Metode**: Penelitian ini menggunakan studi potong lintang dengan melihat hasil pemeriksaan USG transperineal yang dilakukan pada pasien perempuan nulipara, primipara dan multipara yang datang ke poli Obstetri dan Ginekologi RSUPN Dr. Cipto Mangunkusumo pada bulan Mei-Desember 2015. Kami melakukan analisis data dengan SPSS menggunakan one way ANOVA untuk membandingkan area levator hiatal antara kelompok pasien selama manuver Valsalva dan saat istirahat.*

***Hasil**: Terdapat perbedaan bermakna untuk area hiatal otot levator ani pada saat Valsalva maupun istirahat untuk ketiga kelompok penelitian dengan (p=0.028 dan p=0.012). Saat Valsalva, perbedaan area hiatal otot levator ani ditemukan pada kelompok nulipara dan multipara dengan perbedaan rerata (standar deviasi) yaitu 22,26 (5,45) cm^2. Saat istirahat, perbedaan area hiatal otot levator ani ditemukan pada kelompok nulipara dan multipara dengan perbedaan rerata (standar deviasi) yaitu 10,70 (2,26) cm^2. Avulsi otot levator ani terjadi pada 1 dari 46 (2,2%) pada perempuan primipara dan perempuan multipara.*

***Kesimpulan**: Terdapat perbedaan bermakna untuk area hiatal otot levator ani pada saat maneuver Valsalva maupun istirahat untuk ketiga kelompok penelitian.*

[Maj Obstet Ginekol Indones 2016; 4-4: 208-211]

***Kata kunci**: area hiatal levator ani, avulsi, multipara, nulipara, primipara*

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INTRODUCTION

Pelvic floor dysfunction becomes major public health problem, whereas, around 23% of women suffer from this condition worldwide. Pelvic floor dysfunction significantly decreases the quality of life due to many symptoms, such as constipation, urinary or anal incontinence, chronic pelvic pain, and urogenital prolapse.[1]

An important component of pelvic floor system is levator ani muscle; therefore, trauma to this muscle is related to pelvic floor disorders. Avulsion of the levator ani muscle is a common consequence of vaginal childbirth[2] affecting between 13% and 36% of women. In general, it happens after the first vaginal delivery.[2-9] In nulliparas, no avulsions were observed.[10]

A levator avulsion results from the detachment of inferior pubic rami on puborectalis muscle.[11] The striated muscles of levator ani form an essential component of structural support mechanism in the pelvic floor. Unlike other skeletal muscles, the levator ani muscle differs because it maintains constant tone, except during voiding, defecation, and the Valsalva maneuver. It has the capability to con-

tract rapidly during sudden increase of abdominal pressure, for example on a cough or sneeze or physical activity; thereby, it will reduce the risk of incontinence and pelvic organ prolapse (POP). Paradoxically, it has to stretch during parturition even beyond its limits in order to allow the passage of baby. However, it has to contract after delivery to preserve the normal function.[12] Levator anal muscle is very susceptible to the stretch-induced injury. During the stretch, the extent of injury is proportional to the work performed on the muscle.[13] Therefore, this study aims to determine the relationship of the levator hiatal area among nulliparous, primiparous, and multiparous women so that we can assess the prevalence of avulsion.

METHOD

A cross sectional study design was used by evaluating the patients' transperineal ultrasound results. This study used consecutive sampling method with a total of 69 patients. We recruited the women coming to Obstetrics and Gynecology Clinic Dr. Cipto Mangunskusumo hospital from May to December 2015. We exclude the pregnancy women, women with history of pelvic malignancy, history of pelvic reconstructive surgery, history of pelvic trauma, and inability to contract pelvic floor muscles correctly. We described the characteristics demography of women and analyzed using one way ANOVA to compare the levator hiatal dimension among the groups of women during Valsalva maneuver and at rest. We analyzed the data using SPSS.

RESULTS

Of the 69 patients assessed, there were 23 women in each group of nulliparous, primiparous, and multiparous. Demographic characteristics of the patients were presented in Table 1.

Levator hiatal dimension measured at Valsalva maneuver was presented in Table 2. The data distribution on levator hiatal area were normal among all groups. The ANOVA result showed the significant differences on levator hiatal area among nulliparous, primiparous, and multiparous women during Valsalva maneuver (p=0.012).

Table 2. Comparisons of Levator Hiatal Dimensions Measured at Valsalva Maneuver

	N	Mean (SD)	p value
Nulliparous group	23	17.72 (4.93)	0.012
Primiparous group	23	18.69 (5.37)	
Multiparous group	23	22.26 (5.45)	

Table 3 presented levator hiatal dimension measured at rest. Among all groups, levator hiatal measurement was normally distributed. The ANOVA results indicated that there were significant differences on levator hiatal area among nulliparous, primiparous, and multiparous women at rest (p=0.012).

Table 3. Comparisons of Levator Hiatal Dimensions Measured at Rest

	N	Mean (SD)	p value
Nulliparous group	23	10.00 (2.17)	0.028
Primiparous group	23	10.70 (2.26)	
Multiparous group	23	11.96 (2.86)	

Of 46 primiparous and multiparous women, there was 1 (2.2%) patient who developed into levator avulsions. No avulsions were observed in nulliparous women.

DISCUSSION

Levator ani muscle avulsion is common problem in women after vaginal delivery and it is likely to be an etiological factor in the development of female POP, especially cystocele and uterine prolapse.[1]

Table 1. Demographic Characteristics of the Patients

Characteristics	Nulliparous (mean (SD))	Primiparous (mean (SD))	Multiparous (mean (SD))
Age (years)	31.4 (3.2)	27.0 (21.0 - 42.0)*	46.3 (9.5)
Highest birth weight (kg)	-	2.9 (0.6)	3.1 (0.4)
Body mass index (kg/m^2)	23.2 (3.1)	22.8 (3.2)	26.1 (3.7)

Median (min-max)

Acute levator ani muscle injury can be diagnosed clinically through visualization and digital examination; whereas, levator avulsion is associated with large vaginal tear.[2] Chronic detachment of the levator ani muscle from the inferior ramus of pubic bone can be evaluated by palpation.[3]

The incidence of levator ani muscle avulsion following vaginal delivery in our study was around 2.2% and it could be found in primiparous or multiparous women. Previous studies had shown higher incidence rate of levator ani muscle avulsion, namely 36%[4] and 21%[5]. The very low incidence rate in our study might be occurred because we only reported major levator ani muscle avulsion; meanwhile, the minor levator ani muscle avulsion was not counted in.

It is estimated that levator ani muscle injury happens not only during delivery but also during the period of pregnancy. During gestation, the gravid uterus enlarges progressively, inducing its effect on the levator ani muscle, probably through three mechanisms. The mechanisms are an increment of the uterine weight, an elevation of the intraabdominal pressure, and a mechanical interference with its functional activity. Continuously, the uterine weight increases during gestation, reaching its maximum weight during several final weeks of gestation. The levator ani muscle has to bear this weight. At the expense of the levator plate size, the enlarging uterus widens the levator hiatal area progressively. The levator hiatus occupies the anterior part of the levator plate. The lowest part of the enlarging uterus engages through the levator hiatus, resulting progressive widening of the hiatus. Meanwhile, the uterus encroaches on the levator plate, reducing to the minimum its transverse diameter across the pelvic cavity. As a result, the levator plate sags down, leading to suspensory sling subluxation in addition to widening and lowering of the levator hiatus. Hence, most of the anal canal, urethra, and vagina lie above and they are exposed to the direct effect of the intraabdominal pressure. The lowered and widened levator hiatus exposes anal canal and urethra directly to the intra abdominal pressure on straining at defecation or urination. Then, it is transmitted through the abnormally wide levator hiatus to the anal canal and urethra leading to their obstruction. It is predicted that the high anal canal pressure recorded during levator ani muscle contraction on straining in multiparous women coming from the increased intra abdominal pressure directly to the anal canal.[6] The second factor affecting the levator ani muscle during gestation is the constantly increasing intraabdominal pressure induced by the enlarging gravid uterus.[7] Previous studies had stated that the main brunt of the increased intraabdominal pressure fell on the levator plate, particularly on the rectococcygeal raphe, which is the most dependent and durable part of the levator plate.[8-10] Being tendinous, the rectococcygeal raphe and hiatal ligament become overstretched and subluxated. The third factor concerning the effect of the gravid uterus on the functional activity of the levator ani muscle is the mechanical factor. During last month of pregnancy, the gravid uterus mechanically blocks contraction power of the levator ani muscle, leading to interfered contraction process.[6]

According to previous study conducted by Garcia-Mejido[11], the most important risk factor associated with avulsion during vaginal delivery is fetal weight. Some studies had shown that birth weight is a risk factor for pelvic floor damage[12] and urogenital prolapse.[13] However, some studies concluded contrasting results.[14-17] Avulsion leads to an enlargement of the levator hiatus, particularly in its anterior part, which is clearly associated with POP.[20] It has been considered that older age is a risk factor for avulsion.[18-22]

Avulsion occurs more frequently in multiparous compared with nulliparous women due to greater contractibility. Zanetti, et al.[23] found greater distensibility in the multiparous than in the nulliparous women (20.07 (SD 0.46) cm vs 19.3 (SD 2.8) cm; $p<0.001$) during delivery. In addition, previous study conducted by Petricelli, et al.[24] suggested that nulliparous women had higher electrical activity compared to multiparous women. The mechanical and hormonal effects of pregnancy may induce biomechanical, neurological or neuromuscular changes to the pelvic floor and pelvic organ supports[25,26] and they may contribute to pelvic floor dysfunction, independently of delivery mode. Weidner, et al.[27] had demonstrated that pregnancy had negative effect on the electromyographic activity of the urethral rhabdo sphincter.

The limitation of this study included small sample size. The prevalence of avulsion in this study was very low (2.2%); while, the differences between nulliparous and multiparous group could not be observed any further.

CONCLUSION

It is essential to perform the measurement of the levator hiatus in pregnant women. By measuring the levator hiatus, the incidence of POP could be predicted; therefore, preventive management can be held earlier during the process of delivery.

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Research Article

Characteristics of Patients with Obstetric and Gynecologic Fistula in Jakarta

Karakteristik Pasien dengan Fistula Obstetri dan Ginekologi di Jakarta

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Abstract

Objective: To know the characteristics of patients with obstetrics and gynecologic fistula in Dr. Cipto Mangunkusumo Hospital, Jakarta.

Method: This study was a descriptive design using secondary data from medical records and patient database during 2011-2016.

Result: There were 68 subjects with fistula. From 2011-2016, there were 5 cases (7.4%), 19 cases (27.9%), 16 cases (23.5%), 11 cases (16.2%), 8 cases (11.8%), and 9 cases (13.2%) of fistula; respectively. The average age of subjects was 38 years old and only 34 subjects have complete data. Gynecologic and obstetric fistula were 17 cases each. As total 28% of fistula cases were vesicovagina fistula, 12% were rectovaginal fistula, 9% were anovagina fistula, and the other types of fistula were 2%. Among 34 subjects, there were 21% of vesicovagina fistula and 3% of rectovagina fistula, which were caused by iatrogenic. There were 7% of vesicovagina and rectovagina fistula each and 9% of anovagina fistula were caused by obstetric problems. The iatrogenic procedures found from this study were total abdominal hysterectomy (16%), vaginal hysterectomy (3%), and neovagina (3%).

Conclusion: The trend of cases is decreasing during the present years (2011-2016). Gynecologic fistula cases caused by iatrogenic are the major problems, but the obstetrics fistula cases decreasing following the labor monitoring is much better nowadays.

[Indones J Obstet Gynecol 2016; 4-4: 212-217]

Keywords: gynecologic fistula, iatrogenic, obstetric fistula

Abstrak

***Tujuan**: Diketahuinya karakteristik pasien dengan fistula obstetri dan ginekologi di RSCM, Jakarta.*

***Metode**: Studi ini merupakan studi deskriptif dengan menggunakan data sekunder dari rekam medis dan data rekapitulasi pada tahun 2011-2016.*

***Hasil**: Terdapat total 68 subjek yang didiagnosis dengan fistula. Dari tahun 2011 - 2016, terdapat 5 kasus (7,4%), 19 kasus (27,9%), 16 kasus (23,5%), 11 kasus (16,2%), 8 kasus (11,8%), dan 9 kasus (13,2%), berurutan. Usia rata-rata subjek adalah 38 tahun dan hanya 34 subjek yang memiliki data yang lengkap. Fistula ginekologi dan obstetri masing-masing sebanyak 17 kasus. Fistula vesikovagina sebanyak 28%, fistula rektovagina sebanyak 12%, fistula anovagina sebanyak 9%, dan fistula tipe lain sebanyak 2%. Dari 34 subjek, didapatkan fistula vesikovagina (21%) dan rektovagina (3%) yang disebabkan oleh tindakan iatrogenik. Fistula vesikovagina dan rektovagina masing-masing sebanyak (7%) dan anovagina (3%) disebabkan oleh masalah obstetri. Tindakan iatrogenik yang didapat pada studi ini adalah histerektomi total abdominal (16%), histerektomi transvaginal (3%), dan neovagina (3%).*

***Kesimpulan**: Tren jumlah kasus menurun pada saat tahun 2011 - 2016. Fistula ginekologi yang disebabkan oleh tindakan iatrogenik merupakan masalah utama saat ini dibandingkan dengan jumlah kasus fistula obstetri yang menurun seiring pemantauan persalinan yang lebih baik.*

[Maj Obstet Ginekol Indones 2016; 4-4: 212-217]

***Kata kunci**: fistula ginekologi, fistula obstetri, iatrogenik*

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INTRODUCTION

In developing countries, fistula is the conseqence of poor perinatal care. Fistula can be found per 1,000 labors and the prevalence of fistula is around 0.1% to 1.5% per 1000 pregnancies. The major risk factors are early marriage, short stature, poor antenatal care, low socio-economic status, low educational level, and family income or occupation.[1] However, the main factor causing obstetric fistula is obstructed labor. Female who gets fistula will affect their psychosocial status. The psychosocial condition, as mentioned, are divorces (16-92%), socially isolated, the deterioration of poverty, malnutrition, sexual dysfunction, and the disturbance of mental health (anxiety and depression), insomnia, and attempt of suicides.[1]

A study conducted by Waaldjik in Africa showed that the incidence of fistula was 1-2 cases per 1,000 deliveries. The number of incidence represented 50,000-100,000 new cases and the prevalence of fistula could reach 2 million of cases in the world nowadays. In Zambia, there were 259 cases of obstetric fistula, but there were only 95.5% cases of obstetric fistula reported as the consequences of prolonged labor (more than 24 hours). In Ethiopia, around 92% cases of obstetric fistula were related

to poor antenatal care. In Nigeria, there were 85% cases of fistula caused by labored at home.[1]

Based on a study, there were 8.9% to 86% patients with obstetric fistula who were found mostly in teenagers. Besides, around 31% to 66.7% of cases were found in primiparous women. The mean time of labor which increased the risk of fistula was from 2.5 to 4 days. About 20% to 95.7% of women getting the obstetric fistula had prolonged labor (more than 24 hours).[2]

In developing countries, as well as industrial countries, the prevalence of gynecologic fistula is still lowered as compared with obstetric fistula.[1] In developing countries, there are more than 90% of urogenital fistula caused by pelvic surgery. The involvement of urinary tracts is around 1% of gynecologic surgery and caesarean section.[3] There-fore, this study aims to know the characteristics of patients with obstetric and gynecologic fistula in Dr. Cipto Mangunkusumo Hospital.

METHODS

This was a descriptive study design. We recruited samples from secondary data of medical records and patient databases in Division of Urogynecology, Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, between 2011 and 2016. The inclusion criteria were women diag-nosed with fistula during the period of time. The types of fistula were categorized into obstetric and gynecologic fistula. Each of them would be divided into vesicovagina, rectovagina, anovagina, and the other types of fistula. In the age category, it would be divided into 3 groups, such as under 20 years old, 20-35 years old, and above 35 years old.

Perineal laceration would be classified into 2 groups, as mild and severe degree of laceration. Mild degree was defined as first and second degree of perineal laceration. Severe laceration was defined as more than second degree of perineal laceration.

The heaviest birth weight of newborn would be categorized into 3 groups, namely less than 2,500 grams (small), 2,500-4,000 grams (normal), and more than 4,000 grams (large). The risk factor of obstetric fistula would be seen from the procedure and the problem found in this study. It was similar definition for the gynecologic fistula. In this study, all data were processed using SPPS program version 23.0.

RESULTS

The data was obtained during the last 5 years and the results were 68 subjects who were diagnosed with fistula. Of 68 subjects, there were 28% patients of vesicovagina fistula, 11% patients of rectovagina fistula, 9% patients of anovagina fistula, and 2% patients with other types of fistula (urethrovagina, vesicocervicovagina, vesicorectovagina). These number were the summary of both obstetric and gynecologic fistula. The average age of the subjects was 38 years old.

In this study, there were 3 subjects under 20 years old, 29 subjects who were 20 to 35 years old, and 36 subjects who were above 35 years old. Meanwhile, the distribution of nulliparous, primiparous, and multiparous women were 4, 13, and 15 subjects; contributively.

The cases of obstetric fistula had several risk factors including the heaviest birth weight and the degree of obstetrical anal sphincter injuries (OASIS). In this study, there were only 1 subject with history of having labor less than 2,500 grams, 19 subjects of 2,500-4,000 grams, and 3 subjects of above 4,000 grams. Based on the degree of perineal laceration, there were no subjects who had mild degree of perineal laceration (1st degree and 2nd degree of perineal rupture); however, there were 12 subjects who had severe perineal laceration (>2nd degree).

Based on the types of fistula, there were vesicovagina, rectovagina fistula, anovagina, and other types including urethrovagina, vesicocervicovagina, and vesicorectovagina fistula. Among 68 sub-

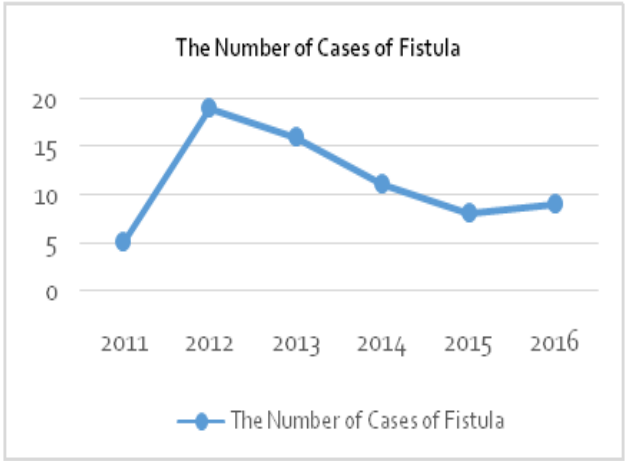

Figure 1. The Trend of Fistula Cases during 2011-2016 in Dr. Cipto Mangunkusumo Hospital.

jects, there were 35 subjects diagnosed as vesicovagina fistula, 17 subjects as rectovaginal fistula, 10 subjects as anovagina fistula, and 6 subjects as other types of fistula.

Fistula is classified as two types, such as obstetric and gynecologic fistula. Obstetric fistula is a fistula caused by obstetric related problems, such as prolonged second stage of labor, perineal laceration, obstetric procedure (caesarean section and assisted vaginal delivery). In this study, among 34 subjects with complete medical records, there were 17 subjects of each case group. From 2011 to 2016, there were 5 (7.4%), 19 (27.9%), 16 (23.5%), 11 (16.2%), 8 (11.8%), and 9 cases; respectively. Actually, the cases in 2006 were less than other years due to the number of months from samples taken, namely between January and March.

Table 1. The Characteristics of Obstetric and Gynecologic Fistula in Dr. Cipto Mangunkusumo Hospital during 2011 to 2016

Variables	N = 68 (%)	
	Obstetric fistula n (%)	**Gynecologic fistula n (%)**
Age		
< 20 years old	1 (2)	0 (0)
20 - 35 years old	13 (19)	3 (4)
> 35 years old	3 (4)	14 (21)
N/A	**34 (50)**	
The types of fistula		
Vesicovagina	5 (7)	14 (21)
Rectovagina	5 (7)	3 (4)
Anovagina	6 (9)	0 (0)
Others	1 (2)	0 (0)
N/A	**34 (50)**	
Risk Factors		
For obstetric		
Caesarean section	3 (4)	
Prolonged second stage of labor	1 (2)	
Assissted/operative vaginal delivery	2 (3)	
Perineal laceration		
Mild	0 (0)	
Severe	12 (18)	
The heaviest birth weight of newborn		
Small (< 2500 grams)	1 (2)	
Normal (2500-4000 grams)	13 (19)	
Large (> 4000 grams)	3 (4)	
Gynecologic procedures/abnormalities		
Transvaginal hysterectomy (TVH)		2 (3)
Total abdomninal hysterectomy (TAH)		11 (16)
Neovagina		2 (3)
Pelvic organ prolapse		2 (3)
Sexual abused		0 (0)
N/A	**34 (50)**	

Among the subjects who had obstetric fistula mostly were in the range of 20 years old until 35 years old. However, there was one subject who had obstetric fistula in the age of under 20 years old. The type of fistula mostly was anovagina fistula, which were found around 6 cases. Meanwhile, vesicovagina and rectovagina fistula were as many as the other types of fistula namely 5 cases.

One of risk factors is obstructed labor. In this study, there was one subject who had obstetric fistula because of prolonged second stage of labor. In addition, assisted vaginal delivery including forceps and vacuum, influenced the fistula formation. This study reported that there were 2 subjects who had obstetric fistula with a previous history of assisted vaginal delivery.

There were 12 subjects with the previous history of severe perineal laceration. In this study, subjects who had severe perineal laceration, mostly had anovagina and rectovagina fistula.

Based on the heaviest birth weight, this study showed that the most cases were found among the subjects having history of delivering 2,500 to 4,000 grams. Nevertheless, birth weight more than 4000 grams affected the fistula formation showed by 3 cases in this study.

Most of the gynecologic fistula cases were found in the age of above 35 years old. Vesicovagina fistula was the most often types of fistula in this study. Gynecologic fistula was mostly affected by gynecologic procedure or iatrogenic. In this study, we found several gynecologic procedures, such as transvaginal hysterectomy, transabdominal hysterectomy, and artificial vagina procedure or neovagina. There were 2 cases due to transvaginal hysterectomy, 11 cases due to transabdominal hysterectomy, and 2 cases because of artificial vagina procedures. There were some gynecologic abnormalities found in this study. They were uterine prolapse and cystorectocele. This study found 2 subjects who had those gynecologic abnormalities. Sexual abuse could be one of the risk factors or the cause of gynecologic fistula called as traumatic gynecologic fistula. However, this study did not find any subjects with the history of sexual abuse.

DISCUSSION

In this study, the average age of the subjects was 38 years old which the most subjects were in the range of 20-35 years old. This corresponded to a study conducted by Kazaura, et al., they stated that there were 334 subjects who had obstetric fistula, 72.2% among them were in the range of 25-29 years old.[4] One meta-analysis study conducted by Ahmed, et al. showed that almost 80% of women had chronic excoriation due to direct irritation by urine.[4]

Fistula tended to interfere women's social and psychosexual life. In a study conducted by Okoyei, et al., women who had fistula had been in emotional instability.[4] However, in this study, we did not do assessment of psychosexual aspects among the subjects.

Especially, obstetric fistula is caused by obstructed labor which happened during full bladder.[5] Early marriage is one of the significant risk factors for the obstetric fistula. Delayed to get married and pregnant will reduce the complications of labor.

In this study, there were 17 cases of obstetric fistula, caused by prolonged second stage of labor and assissted vaginal delivery (forceps or vacuum). There were several primary risk factors, such as the duration of labor, the facilities and the health workers, partograph, poor antenatal care, early marriage, and aging population. A study conducted by Unfer, et al. showed that there was higher incidence of obstetric fistula among women delivering low birth weight baby, especially in teenage population. The increasing obstetric risk in teenage is due to immaturity of anatomical structure on pelvic organ and bone.[2]

The teenage pregnancy has the highest prevalence in developing countries (7-30%) and it is associated with the incidence of cephalopelvic disproportion.[6] One of the strategies to reduce obstetric fistula is through prevention of teenage pregnancy. Women who have height under 155 cm and the age under 19 years old have 4.9 times higher risk in caesarean section.[6] Regardless, caesarean section will increase the maternal and fetal outcomes in obstructed labor.[6]

The obstructed labor has been the major cause of maternal morbidity, such as infection and obstetric fistula. The obstructed labor is a mechanical process affected by the fetal size and malpresentation. According to World Health Organization (WHO), prolonged labor is defined as the labor taking place more than 18 hours. The formation of fistula is commonly found among primigravid patients. A case study conducted in Addis Ababa,

Africa, there were 97% of vesicovagina fistula caused by obstructed labor, whereas 65% occurred among subjects in the age of under 25 years old, and 63% were primigravid.[7] This was different from our study, which the proportion of fistula is commoner in multiparous than primiparous women. Vesicovagina fistula or obstetric fistula is caused by ischemic necrosis process of bladder tissue and vagina, which are trapped between the head of the fetus and the symphisis of maternal during the obstructed labor. Actually, it can impact to rectovagina fistula, in spite of very rarely condition.[7] In case series conducted by Kano, in Sub-Saharan Africa, there were 120 subjects who had been diagnosed as vesicovagina fistula and most of them had early marriage. In Sokoto, same case series, there were 93.6% of the subjects having marriage before 18 years old. Obstetric fistula was mostly found in the age of 20 to 29 years old. Primiparous was the major group who had been diagnosed as vesicovagina fistula.[8]

The most common cause of non obstetric fistula or gyencologic fistula is iatrogenic procedure, such as pelvic surgery, trauma of the genital (coitus, sexual abused, accident, and genital mutilation), granulomatous infection, tuberculosis, and HIV. Not only those, but also there are congenital malformation, cancer especially cervical cancer with or without radiotherapy which influence to the occurrence of this fistula.[9] In this study, among the 34 subjects, there were no subjects with the history of infection as well as cancer.

The gynecologic procedures in this study were total vaginal hysterectomy, total abdominal hysterectomy, and artificial vagina or neovagina. Abdominal hysterectomy surgery has the higher risk than vaginal hysterectomy in the formation of fistula. However, we did not find the incidence of fistula in supracervical hysterectomy. Meanwhile, gynecologic abnormalities of genital, such as uterine prolapse, were rarely found to be the cause of fistula. Nevertheless, if there are gynecologic abnormalities, they are usually associated with trauma, such as erosion caused by inserting pessary around vaginal wall near bladder. Iatrogenic urogenital fistula can be the result of pelvic surgery and radiotherapy which are associated with tissue damage.[10]

The most common type of iatrogenic fistula is vesicovagina fistula seen in our study. There were 14 cases out of 17 cases of vesicovagina fistula. A study reported that the prevalence of vesicovagina fistula caused by iatrogenic procedures was 60 to 75% by hysterectomy in non malignant cases, 30% by hysterectomy in malignant cases, and 6% by caesarean section.[11] The risk of fistula formation of the pelvic organ associated with hysterectomy was 0.1% to 4%. In a retrospective study in USA, they showed that gynecologic fistula caused by gynecologic procedure was 82%, 8% due to the obstetric procedure, and also 6% because of radiation.[11] The incidence of genitourinary fistula caused by abdominal hysterectomy in non malignant cases was 1 from 1,000 cases. The degree of bladder injury is the main factor of the fistula formation.[11] In a study, where there were 1,317 cases of hysterectomy in non malignant subjects, there were 46% abdominal hysterectomy, 48% vaginal hysterectomy, and 6% of them were performed by laparoscopy. All of them had become the risk factor of vesicovagina fistula followed by intraoperative injury of the bladder.[11]

Abdominal hysterectomy in non malignant cases was the second commonest cause (21.6%) of gynecologic fistula, while vaginal hysterectomy, radical hysterectomy, and laparoscopic hysterectomy were 10.8%, 5.4%, and 2.7%, respectively.[12] Laparoscopic hysterectomy has the highest incidence in bladder injury. However, in this study, abdominal hysterectomy has the largest proportion of cases than vaginal hysterectomy. In addition, there was one case of gynecologic fistula caused by hysterectomy followed by salphingectomy, as the underlying problem was ovarian cyst. This study also found that there were 3 cases of fistula with the previous history of caesarean section. Caesarean section has not been the direct cause of the fistula formation but the indication of this procedure should be considered. Indication of caesarean section could be due to fetal distress and obstructed labor itself which will be related to obstetric fistula. However, there are several caesarean section procedures which can be the main cause of the fistula formation because either there is prolonged and directed pressure on the bladder during the procedure or imperfect closing of the wound.

The strength of this study is the data which were obtained more than 5 years. Especially, this will be enough to represent the prevalence and incidence of fistula in Dr. Cipto Mangunkusumo Hospital. This study can be as the reference of the other studies.

The limitation of this study is that there were some incomplete data regarding the subjects.

CONCLUSION

The number of fistula cases are similar among obstetric and gynecologic fistula during 5 years. The trend of these cases is decreasing concomitant to the improvement of technology and surgeon's skill. In this study, obstetric fistula cases are caused by prolonged second stage of labor, operative or assisted vaginal delivery, and severe degree of perineal laceration. Although, gynecologic fistula cases are mostly caused by hysterectomy or iatrogenic procedures and they still become the major problem nowadays. Nevertheless, obstetric fistula cases are decreasing in accordance with good labor monitoring.

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Research Article

Perineal Massage during Second Stage of Labor to the Perineal Laceration Degree in Primigravida

Efek Masase Perineum Kala Dua Persalinan terhadap Derajat Laserasi Perineum pada Primigravida

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Abstract

Objective: To determine the effect of perineal massage during second stage of labor on the perineal laceration degree in primigravida.

Methods: The design of this study was non randomized controlled trial by conducting massage training of the perineum to 20 obstetrics and gynecology residents. All residents had passed the normal delivery care training. Primigravida who met the inclusion criteria were included in this study. We assessed the degree of perineal laceration in this study. Data were analyzed using Chi square test in SPSS.

Results: We obtained 103 subjects for massage group and 79 subjects for control group. There was a significant association between massage group and the incidence of intact perineum. In the massage group, most of perineal lacerations were first degree of laceration (52.4%); whereas, in the control group, most of them were second degree of laceration (77.2%). Statistical analysis showed a significant association between perineal massage and decreased of perineal laceration degree ($p<0.05$).

Conclusion: Perineal massage during second stage of labor in primigravida can reduce the degree of perineal laceration.

[Indones J Obstet Gynecol 2016; 4-4: 218-221]

Keywords: degree of perineal laceration, perineal massage, primigravida, second stage of labor

Abstrak

***Tujuan**: Untuk mengetahui efek masase perineum pada kala II persalinan terhadap derajat laserasi perineum pada primigravida.*

***Metode**: Penelitian ini menggunakan desain uji coba terkontrol tidak acak. Dilakukan pelatihan masase perineum terhadap 20 orang residen obstetri dan ginekologi (semua residen telah mengikuti pelatihan Asuhan Persalinan Normal). Primigravida yang memenuhi kriteria inklusi diikutsertakan dalam penelitian. Kami melakukan penilaian derajat laserasi perineum pada kasus penelitian. Data dianalisis dengan uji Chi square.*

***Hasil**: Dari 182 sampel, didapatkan 103 sampel untuk kelompok masase dan 79 sampel kelompok kontrol. Terdapat hubungan yang bermakna antara perlakuan masase perineum dengan keutuhan perineum. Pada kelompok masase, mayoritas derajat laserasi adalah laserasi tingkat 1 (52,4%), sedangkan pada kelompok kontrol mayoritas derajat laserasi adalah laserasi tingkat 2 (77,2%). Hasil uji statistik menunjukkan hubungan yang bermakna antara masase perineum dan penurunan derajat laserasi perineum ($p<0,05$).*

***Kesimpulan**: Masase perineum kala II persalinan pada primigravida dapat menurunkan derajat laserasi perineum.*

[Maj Obstet Ginekol Indones 2016; 4-4: 218-221]

***Kata kunci**: derajat laserasi perineum, kala II persalinan, masase perineum, primigravida*

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INTRODUCTION

During delivery process, women had risk for perineal trauma, especially in the first labor. As many as 60% of women have ever experienced perineal trauma in vaginal delivery and at least 1,000 women require perineal suturing after childbirth. Birth canal trauma is caused by episiotomy, spontaneous perineal laceration, forceps trauma, extraction vacuum or extraction version.[1,2]

Study in UK showed that 85% of women who undergo vaginal delivery got perineal trauma and two-third of them had to do perineal suturing. Three million vaginal deliveries of women were generally experienced perineal trauma caused by spontaneous rupture and episiotomy in the United States. Complications occured in perineal trauma include bleeding, hematome, abscess, perineal pain, fistula, dyspareunia, and alvi incontinence.[1,3,4]

There is strong evidence that episiotomy is ineffective to prevent complications from delivery. Thacker and Banta in 1983 questioned the benefit of routine episiotomy. Since 1860 to 1980, the incidence of third and fourth degree of perineal rupture in women without episiotomy was between 0 and 6.4% compared with the women

with episiotomy, including from 0 to 23.9%. Their result did not point out the benefit of episiotomy in terms of reducing the incidence of urinary and alvi incontinence.[1,5]

Perineal pain was reported more intense immediately after postpartum and continued until two-week postpartum in 30% of women; even, 7% of women experienced the pain up to three-month postpartum. Women delivering vaginally without perineal trauma or with perineal trauma had several advantages, such as shorter length of stay, better pelvic floor muscle strength and sexual function, also low level of depression and perineal pain. Perineal trauma could also cause discomfort and pain during sexual intercourse.[6,7]

Perineal massage is one of the ways to increase blood flow, elasticity, and relaxation of the pelvic floor muscles. It can soften the perineal tissue; thus, it will open without resistance during childbirth. Perineal massage is able to reduce the risk of perineal trauma or the need for episiotomy at primigravida.[7]

Study by Geranmayeh and Karacam reported that the decrease of perineal laceration degree and episiotomy rate in primigravida was because of perineal massage performing in the second stage of labor. However, a study by Stamp concluded that perineal massage in the second stage did not have significant impact on the degree of perineal laceration and perineal pain after delivery.[8,9]

Study about perineal massage antepartum on primigravida had been held in Makassar; no studies focused on perineal massage in the second stage of labor in primigravida, yet. Therefore, this study aims to determine the effect of perineal massage during second stage of labor to the degree of perineal laceration in primigravida.

METHODS

We used non-randomized controlled trial study. The study was conducted in several teaching hospitals of Obstetrics and Gynecology Department, Faculty of Medicine Universitas Hasanuddin, Makassar from August 2014 to February 2015. We recruitted all primigravidas who had delivery in several teaching hospitals of Obstetrics and Gynecology Department, Faculty of Medicine Universitas Hasanuddin, Makassar. The subjects who met the inclusion criteria were asked for the approval participation in the informed consent. We assessed the qualified subjects in appropriate to the criteria. The data were analyzed using Chi square and Krustal-Wallis test in SPSS. The Chi square analysis was used to determine the difference between perineal status on treatment or control group during second stage of labor. Mean while, Krustal-Wallis test aimed to assess the difference on perineal laceration degree between study and control group. The result was considered significantly if p less than 0.05.

RESULTS

This study was conducted from August 2014 to February 2015 to determine the effect of perineal massage during second stage of labor to the perineal laceration degree in primigravida. We obtained 182 subjects divided into two groups: 103 subjects in massage group and 79 subjects as control group.

Table 1 showed the characteristics of the subject distribution. Both massage and control group consist of women under 30 years old (545% VS 45.5%). Women with low educational background were 26 cases (53.0%) on massage group and 23 cases (47.0%) were not performed the massage; while, for high educational background, there were 77 cases (57.9%) in massage group and 56 cases (42.1%) in control group. Most of women had occupation both in massage and without massage group. According to income, there were 75 cases (60.0%) with massage and 50 cases (40.0%) without massage in high income group and 28 cases (49.1%) with massage and 29 cases (50.9%) without massage in low income group. Chi square test concluded that there were not significant differences in each characteristic of subject including age, education, occupation, and income.

Table 1. Characteristics of the Subject

Characteristics	Massage (+) (%)	Massage (-) (%)	p
Age (years old)			
< 30	85 (54.5)	71 (45.5)	0.180
> 30	18 (69.2)	8 (30.8)	
Education			
Low	26 (53.0)	23 (47.0)	0.550
High	77 (57.9)	56 (42.1)	

Occupation			
Yes	84 (54.9)	69 (45.1)	0.290
No	19 (65.5)	10 (34.5)	
Income			
High	75 (60.0)	50 (40.0)	0.170
Low	28 (49.1)	29 (50.9)	

**Chi square test*

Table 2 indicated the result on comparative analysis of perineal status between perineal massage and control (without perineal massage) group. Of Table 2, perineal status on women in perineal massage group remaining intact and laceration was 43 (41.7%) and 60 (58.3%). Perineal status in control group who kept intact and laceration was on 4 women (5.1%) and 75 women (94.9%). Result of chi-square test indicated that there was a relationship of perineal massage during second stage labor and perineal status (p<0.001).

Table 3 showed the result on comparative analysis of the perineal laceration degree between perineal massage and control group. In this study, for perineal massage group, the percentage of perineal laceration on first, second, third, and fourth grade was 52.4%, 5.8%, 0%, and 0%; respectively. Meanwhile, in control group, the percentage of laceration on first, second, third, and fourth degree was 16.4%, 77.2%, 1.3%, 0%; contributively. There was an association between perineal massage during second stage of labor and the degree of perineal laceration (p<0.001).

DISCUSSION

The characteristics of subjects showed in terms of age, education, occupation, and income were not statistically significant with p more than 0.05. therefore, we considered the subjects between groups were nomogenaus. In Table 2, we got p value less than 0.05 for the comparison of perineal status between the perineal massage and control group. In Table 3, the comparison degree of perineal laceration between the perineal massage and control group resulted p value less than 0.05. Therefore, our result concluded that the perineal massage can reduce the degree of perineal laceration.

Massage aims to relieve pain, produce relaxation, and reduce stress caused by the labor process.[10] In this study, 41.7% perineum remained intact on the massage group; while, there were only 5.1% of subjects had intact perineum in control group. A study by Labrecque stated that of 283 primigravida undergoing perineal massage, there was 24.5% perineum kept intact compared to primigravida who did not get perineum massage which showed only 15.1%.[11]

Table 2. Comparative Analysis of Perineal Status between Perineal Massage and Control Group

	Perineum Intact (+)		**Perineum Intact (-)**		**Total**	**p**
	N	%	N	%	N	
Massage (+)	43	41.7	60	58.3	103	<0.001
Massage (-)	4	5.1	75	94.9	79	
Total	47	28.8	135	74.2	182	

**Chi square test*

Table 3. Comparative Analysis of the Degree of Perineal Laceration between Perineal Massage and Control Group

	Degree of Laceration					**Total**	**p**
	Intact	**Level 1**	**Level 2**	**Level 3**	**Level 4**	**N**	
Massage (+)	43	54	6	-	-	103	<0.001
	41.7	52.4	5.8	0	0		
Massage (-)	4	13	61	1		79	
	5.1	16.4	77.2	1.3	0		
Total	47	67	67	1	0	182	

**Krustal-Wallis test*

In this study, for perineal massage group, the percentage of perineal laceration on the first, second, third, and fourth grade was 52.4%, 5.8%, 0%, and 0%; respectively. Meanwhile, in control group, the percentage of laceration on the first, second, third, and fourth degree was 16.4%, 77.2%, 1.3%, 0%; contributively. This result was in appropriate to study by Sofian Muhaji in 2002. They explained that the perineal massage group tended to have lower degree of perineal laceration, especially on the first grade (96.7%). Study by Geranmayeh and Karacam in 2012 recorded the similar result that in the perineal massage group, the patients had more first degree of perineal laceration (42.9%) compared to higher degree of laceration during second stage of labor.[8,12]

CONCLUSION AND SUGGESTION

In conclusion, perineal massage on the second stage of labor in primigravida can reduce the degree of perineal laceration. Further studies should be held to compare the effectiveness of perineal massage on antenatal and during second stage of labor.

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Research Article

A Simple Ultrasound Examination as Diagnostic Tool for Malignant Ovarian Tumor

Pemeriksaan Ultrasonografi Sederhana sebagai Alat Diagnostik Tumor Ovarium Ganas

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Abstract

Objective: To know the diagnostic value of simple ultrasound examination to detect malignant ovarian tumor.

Method: This study used cross-sectional design in gynecology outpatient clinic at Dr. Cipto Mangunkusumo Hospital. We recruited the patients with ovarian tumor undergoing surgery between March and July 2015. Samples were taken using consecutive sampling. Analysis was done using Chi-square test and logistic regression to find the relationship between ultrasound morphologic patterns with histopathologic findings, where the significant relationship was p value less than 0.05. Furthermore, a model derived from logistic regression was made to calculate the probability having ovarian malignancy.

Result: There were 80 subjects which 58 subjects (72.5%) had benign tumor and 22 subjects (27.5%) had malignant tumor. Ultrasound examination result using ≥ 2 morphologic patterns gave malignant result in 53.8% subjects with the sensitivity of 100%, specificity of 82.8%, positive predictive value of 68.8%, and negative predictive value of 100%. The most important patterns were irregular internal cyst wall, multilocular, presence of papillary projection, and presence of solid component. The probability of subject having ovarian malignancy with ≥ 3 morphologic patterns was more than 88.9%.

Conclusion: Simple ultrasound examination can be used to detect malignant ovarian tumor.

[Indones J Obstet Gynecol 2016; 4-4: 222-226]

Keywords: diagnostic, histopathology, morphology pattern; ovarian tumor; ultrasonography

Abstrak

***Tujuan**: Mengetahui nilai diagnostik pemeriksaan ultrasonografi sederhana dalam menilai keganasan tumor ovarium dibandingkan hasil histopatologi pascaoperasi.*

***Metode**: Penelitian ini merupakan studi potong lintang pada pasien tumor ovarium di polikinik Ginekologi RSCM Jakarta yang dilakukan operasi pada bulan Maret-Juli 2015. Sampel penelitian diambil dengan metode consecutive sampling. Analisis menggunakan uji Chi-square dan regresi logistik untuk mencari hubungan antara pola morfologi ultrasonografi dengan hasil histopatologi di mana terdapat hubungan bermakna apabila nilai p<0,05. Selain itu, dibuat model persamaan dari regresi logistik untuk menghitung probabilitas.*

***Hasil**: Terdapat 80 subjek penelitian di mana 58 subjek (72,5%) dengan tumor jinak dan 22 subjek (27,5%) dengan tumor ganas. Hasil ultrasonografi dengan pola morfologi ≥ 2 menunjukkan hasil ganas pada 53,8% subjek dengan nilai diagnostik sensitivitas 100%, spesifisitas 82,8%, nilai duga positif 68,8%, dan nilai duga negatif 100%. Pola morfologi yang paling berpengaruh terhadap keganasan tumor ovarium adalah permukaan dalam dinding kista reguler, multilokular, terdapat penonjolan papiler, dan ada bagian padat dalam tumor. Probabilitas subjek mendapat tumor ganas apabila memiliki pola morfologi ≥ 3 adalah lebih dari 88,9%.*

***Kesimpulan**: Pemeriksaan ultrasonografi sederhana dapat digunakan untuk mendeteksi keganasan tumor ovarium.*

[Maj Obstet Ginekol Indones 2016; 4-4: 222-226]

***Kata kunci**: diagnostik, histopatologi, pola morfologi, tumor ovarium, ultrasonografi*

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INTRODUCTION

Ovarian cancer is the fourth rank of cancer among women in developed country.[1] In Indonesia, ovarian cancer is the third most often malignancy in women after cervical and breast cancer.[2] Based on the recent world's estimation, there are 204,449 new cases annually, in which it contributes to 124,860 deaths associated with ovarian cancer.[3] Ovarian cancer is considered as a silent killer. Five-year-survival rate depends on the stage of cancer.[4,5] Among all gynecology cancers in Indonesia, the death rate of ovarian cancer is around 22.6%. Approximately 42.5% of ovarian cancer patients seek treatment when already in stage II-IV. About 70-80% of advanced stage ovarian cancer has spread widely and goes through metastasis. Five-year-survival rate of ovarian cancer is 72.8% in stage I, 46.3% in stage II, 17.2% in stage III, and only 4.8% in stage IV.[5]

A high mortality rate is due to the difficulty to detect the early-stage of ovarian cancer. Therefore, holistic approach need to be done to reduce mortality. The ovarian cancer can be diagnosed from comprehensive history taking by exploring the symptoms, potential risk factors, and family history.[6] According to Olson et al. in 2001,[7] the ovarian malignancies does not present specific complaint and they often misleading with dyspepsia syndrome in primary health care. Furthermore, we should do the physical examination; however, it has poor sensitivity in diagnosing the ovarian cancer around 15-51%.[6]

Ultrasound is the best tool to predict ovarian malignancy with the sensitivity of 80-100%.[8] Galvan, et al. concluded that ultrasound examination (sensitivity 98.6%; specificity 94.9%) was better than history taking (sensitivity 79.5%; specificity 96.2%) and pelvic physical examination (sensitivity 97.3%; specificity 85.9%).[9] In order to screen ovarian malignancy, morphological evaluation was performed in accordance to study by Galvan, et al.[9], Sassone, et al.[10], Ferrazzi, et al.[11] International Ovarium Tumor Analysis (IOTA)[12] stated that the criteria to detect the malignant ovarian tumor should be seen from several aspects, such as bilateral symmetry, wall thickness (thin ≥ 3mm, thick > 3mm), wall surface (regular/irregular), septation (thin ≥ 3mm, thick > 3mm), papillary projection, solid area (not present, present ≤ 1x1 cm in internal wall surface), ascites, echogenicity (cystic/solid), acoustic shadow (present/not present), if Doppler examination is available, neovascularization can be examined with resistance index (<0.41).

Unfortunately, in Indonesia, ultrasound examination has not become a standard procedure in primary health care. In primary health care, ultrasound examination is usually performed to screen obstetric problem not in gynecologic problem. In order to reduce mortality rate of ovarian cancer, screening is necessary in primary health care. This study aims to evaluate the use of simple ultrasound examination in assessing ovarian tumor in Indonesia. In the future, it is expected that ultrasound examination can be a routine diagnostic tool for ovarian cancer screening in primary health care.

METHODS

This study was descriptive analytic with cross sectional design using secondary data from medical records in Dr. Cipto Mangunkusumo hospital. Samples were taken using consecutive sampling. The inclusion criteria were patients suspected ovarian neoplasm in Dr. Cipto Mangunkusumo Hospital that undergone operative procedure from March to July 2015 and those patients had a complete medical record to be further investigated. Simple ultrasound morphologic patterns analyzed were bilateral symmetry, wall surface, unilocular/multilocular cyst, presence of solid area, and ascites. These simple ultrasound morphologic patterns were compared with the histopathology results post surgery. We excluded the patients if the history data from histopathology and ultrasound examination were not complete, post chemotherapy in advanced stage of ovarian cancer, solid ovarian neoplasm, and dermoid cyst.

The collected data were statistically analyzed with SPSS version 21.0. Analysis was done using Chi-square test and logistic regression to find the relationship between ultrasound morphologic patterns and histopathologic findings. We considered the significant relationship when p value was less than 0.05. We searched for the specificity, sensitivity, positive and negative predictive value, positive and negative likelihood ratio, and the accuracy. Furthermore, a model derived from logistic regression was made to calculate the probability having ovarian malignancy. This study has been approved by the Committee Ethic of RSCM on No. 711/ UN2.F1/ETIK/2015.

RESULTS

There were 101 patients diagnosed with ovarian neoplasm and we excluded 21 patients; therefore, the number of subjects analysed in this study were 80 subjects. The mean age of the subjects was 39.1 (SD 12.4) years old. The age of malignant group was older than benign group (44 vs 36 years old). Forty-five percent of the subjects were nullipara. The commonest symptom felt by subjects was abdominal enlargement (76.3%). The median level of CA-125 was higher in malignant group compared with benign one (247 U/ml vs 127 U/ml).

The histopathology results showed that 27.5% was malignant with mucinous cystadenocarcinoma (10%) at most. While, of the benign group, endometriosis cyst (35%) was the highest prevalence. There was significant relationship between morphologic patterns from ultrasound and histopathology results (p<0,001). If we used ≥ 2 ma-

lignant morphologic patterns found, the sensitivity 100%, specificity 82.8%, positive predictive value (PPV) 68.8% and negative predictive value (NPV) 100%. Whereas, if we used ≥ 3 malignant morphologic patterns, the sensitivity, specificity, PPV, NPV were 77.3%, 89.7%, 73.9%, 91.2%; consecutively.

There was significant relationship between histopathology results and morphologic patterns of ultrasound, such as wall irregularity (p<0.001), multilocular (p=0.002), papillary projection (p=0.004), presence of solid part (p<0.001), and ascites (p=0.008). There was no significant relationship between histopathology result and bilateral symmetry (p=0.137) (shown on Table 1). After all the data had been collected, all variables with p value < 0.25 in the bivariate analysis was inserted to multivariate analysis (shown on Table 2). The result explained that morphologic patterns that influenced the malignancy together were wall irregularity, multilocular, papillary projection, and presence of solid part.

with the probability of each subject having the outcome of ovarian malignancy was calculated by:

$$p = 1/(1 + e(-y))$$

Table 3. Probability of the Subjects to Become Ovarian Neoplasm Correlated with Type and Number of Morphologic pattern

Variable	y	P
(A) Wall iregularity	-3.452	3.1%
(B) Multilocular	-3.993	1.8%
(C) Papillary projection	-3.021	4.6%
(D) Solid area	-3.203	3.9%
A + B	-1.079	2.4%
A + C	-0.107	47.3%
A + D	-0.289	42.8%
B + C	-0.648	34.3%
B + D	-0.830	30.4%
C + D	0.142	53.5%
A + B + C	2.266	90.6%
A + B + D	2.084	88.9%
A + C + D	3.056	95.5%
B + C + D	2.515	92.5%
A + B + C + D	5.429	99.6%

Table 1. Diagnostic Value of Ultrasound Morphologic Pattern.

Morphologic pattern	Diagnostic value							
	P	Sens	Spec	PPV	NPV	LR+	LR-	Accuracy
Uni/bilateral	0.137	54.5%	63.8%	36.4%	78.7%	1.51	0.71	61.3%
Wall surface	<0.001	54.5%	94.8%	80.0%	84.6%	10.55	0.48	83.8%
Locus	0.002	63.6%	74.1%	48.3%	84.3%	2.46	0.49	71.3%
Papillary projection	0.004	31.8%	94.8%	70.0%	78.6%	6.15	0.72	77.5%
Solid area	<0.001	90.9%	77.6%	60.6%	95.7%	4.06	0.12	81.3%
Ascites	31.8%	31.8%	93.1%	63.6%	78.3%	4.61	0.73	76.3%

**Sens = sensitivity*
**Spec = specificity*
**PPV = positive predictive value*
**NPV = negative predictive value*
**LR (+) = ikelihood ratio (+)*
**LR (+) = likelihood ratio (-)*

Table 2. Multivariate Analysis of Ultrasound Morphologic Pattern and Histopathology Result

Variable	p value	OR	95% CI
Wall surface	0.010	18.42	2.02 - 167.93
Locus	0.019	10.73	1.47 - 78.37
Papillary projection	0.011	28.37	2.14 - 375.43
Solid area	0.009	23.64	2.19 - 254.73

We got the equation model that obtained from multivariate analysis with

y = -6,366 + 2,914 (Irregular of the wall) + 2,373* (multilocular) + 3,345* (presence of papillary projection) + 3,163* (solid area)*

Table 3 showed that the greatest probability of the morphologic pattern leading to malignancy; while, if it appeared alone, the highest chance of being ovarian neoplasm was papillary projection (4.6%) followed by solid area (3.9%). If there were 2 morphologic patterns, the probability of malignancy was ranged from 25.4% to 53.3%. If there were 3 morphologic patterns, the probability of malignancy was increased between 88.9% and 95.5%. If the subjects had 4 morphologic patterns, the probability was almost perfect (99.6%).

DISCUSSION

The mean age of the subjects was 39.2 (SD 12.4) years old with the age of malignant group was older than benign group (44 vs 36 years old). The result was similar to study conducted by Yazbek, et al. in King's College Hospital, London. The mean of patient's age with malignancy was 52 years old and the mean of patient's age with benign adnexa tumor was 39 years old.[13] As in literature, the risk of malignancy in ovarian neoplasm was higher as the increasing of age.

The median of labor history was once (0-5 times) with 45% of them were nullipara. Similar to Goff, et al. study, there were 1,709 subjects; whereas, 48% of them were nullipara.[14] Continuous ovulation associated with nulliparity increases the risk of ovarian malignancy because every ovulation cycle will induce invagination and damage to the surface of epithelial cell.

The commonest symptom was abdominal enlargement (76.3%) in malignant group (95.5%) and benign group (69.0%). This result was similar to Goff, et al. study from 128 women (84 benign tumor and 44 malignant tumor), the most often complaint was bloating (70%) followed by abdominal enlargement (64%).[14] Symptom of ovarian neoplasm was not specific; thus, ovarian malignancy was difficult to detect in early stage.

Level of tumor marker CA-125 in malignant tumor had a median of 247 U/ml; while, the benign tumor was 127 U/ml. Similar result obtained in a retrospective study by Bouzari Z, et al. on 182 women that the level of CA-125 as the tumor marker was higher in cases with malignant ovarian tumor than benign. Bouzari, et al. found that the cut-off point of CA-125 (88 U/ml) would offer the sensitivity of 88%, specificity of 97%, positive predictive value of 84% and negative predictive value of 99%.[15]

The histopathology results described that 27.5% was malignant with mucinous cystadenocarcinoma (10%) at most. While from the benign group, endometriosis cyst (35%) was the most often. This result was not much different from Timmerman D, et al. study on 1,066 subjects; 27% of them were malignant.[12]

There was significant relationship ($p<0.001$) between morphologic patterns from ultrasound and histopathology results. If using ≥ 2 malignant morphologic patterns found that sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 100%, 82.8, 68.8%, 100%; respectively. While finding ≥ 3 malignant morphologic patterns, the sensitivity, specificity, PPV, NPV were 77.3%, 89.7%, 73.9%, 91.2%; respectively. Similar result was obtained in the study by Hafeez S, et al., the sensitivity of ultrasound in detecting ovarian malignancy was 93%, specificity 89%, positive predictive value 91%, negative predictive value 89% and the accuracy reached 91%.[8]

From bivariate analysis, there was significant relationship between histopathology results and morphologic patterns of ultrasound, such as wall irregularity ($p<0.001$), multilocular ($p=0.002$), papillary projection ($p=0.004$), presence of solid part ($p<0.001$), and ascites ($p=0.008$). There was no significant relationship between histopathology results and bilateral symmetry ($p=0.137$). All variables with p value < 0.25 in the bivariate analysis was inserted into multivariate analysis, in which the morphologic pattern that influenced the malignancy were wall irregularity, multilocular, papillary projection, and presence of solid part. Similar result was shown by the study of Timmerman, D et al. which found a significant relationship between morphology patterns from ultrasound in ovarian neoplasm, such as ascites, irregularity of wall, papillary projections, bilateral symmetry, septum, and acoustic shadow and the results of histopathology ($p<0.01$). A significant relationship was also found in multilocular with solid parts ($p <0.01$), unilocular with solid parts ($p = 0.02$), multilocular and unilocular without solid part ($p <0.01$), and the presence of the solid part ($p <0.01$).[12] This study found that no significant relationship in bilateral symmetry pattern, this was due to many benign tumors in this study had bilateral pattern (63.6%).

In this study, the presence of solid part had the highest sensitivity (90.9%), while the highest specificity was wall irregularity and papillary projection (94.8%). The best positive predictive value was wall irregularity (80%) and the best negative predictive value was presence of solid part (95.7%). The highest accuracy rate was wall irregularity (83.8%). The greatest probability of the morphologic pattern leading to malignancy while appearing alone was papillary projection 4.6% followed by presence of solid part 3.9%. If there were 2 morphologic patterns, the probability of malignancy was ranged from 25.4% to 53.3%. If there were 3 morphologic patterns, the probability

of malignancy was increased between 88.9% and 95.5%. If the subjects had 4 morphologic patterns, the probability was 99.6%. The diagnostic value of morphologic pattern in Timmerman D, et al. study (1,066 subjects with adnexal tumor), found the highest sensitivity was the presence of solid part (91.8%), while the highest specificity was ascites (96.1%).[12] Factors in Timmerman study correlating to ovarian malignancy using logistic regresion were age, history of ovarian tumor in family (OR 4.95), diameter of tumor, diameter of solid part, presence of ascites (OR 4.72), presence of blood flow in papilarry projection (OR 3.23), presence of solid part (OR 2.53), wall iregularity of the cyst (OR 3.13).[12,16] In study by Timmerman, et al., they included demographic characteristics and ultrasound result as the malignancy predictor in ovarian neoplasm; meanwhile, in this study, we only recruitted the ultrasound patterns. Based on that, we found similar result where the presence of solid components and irregular internal wall surface of the cyst tended to malignancy.[16]

CONCLUSION

In order to reduce mortality rate of ovarian cancer, screening is necessary in primary health care. Simple ultrasound examination is a great diagnostic tool which has high sensitivity and specificity in diagnosing ovarian malignancy

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Research Article

Efficacy and Safety of Cryotherapy in "See and Treat" Program in Jakarta Primary Health Centre

Efektivitas dan Keamanan Krioterapi pada Program See and Treat di Puskesmas Wilayah Jakarta

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Abstract

Objective: To evaluate the efficacy and safety of cryotherapy in "See and Treat" program in Jakarta Primary Health Care.

Method: Using descriptive cross-sectional design, data from medical records were taken with total sampling method. We took the VIA result, cryotherapy procedure, first-marriage age, number of marriage, parity, smoking habit, and the use of contraception. Data were analyzed univariately.

Result: Of 86 data, the percentage of cryotherapy to change from positive to negative of VIA result was 90.70%. We did not find the progressivity to invasive cancer.

Conclusion: Cryotherapy is effective to manage the cervical pre-cancerous lesion in "See and Treat" program.

[Indones J Obstet Gynecol 2016; 4-4: 227-233]

Keywords: cryotherapy, Indonesia, see and treat, visual inspection of acetic acid (VIA)

Abstrak

***Tujuan**: Untuk mengevaluasi efektivitas dan keamanan krioterapi pada program "See and Treat" di Puskesmas wilayah Jakarta.*

***Metode**: Dengan desain deskriptif potong lintang, data dari rekam medis diambil dengan metode total sampel. Variabel yang dicatat adalah hasil IVA, tindakan krioterapi, usia pertama menikah, jumlah pernikahan, paritas, kebiasaan merokok, dan penggunaan kontrasepsi. Data dianalisis secara univariat.*

***Hasil**: Dari 86 data yang dianalisis, persentase keberhasilan krioterapi dalam konversi hasil IVA mencapai 90,70%. Kami tidak mendapatkan progresivisitas menjadi kanker invasif.*

***Kesimpulan**: Krioterapi efektif dan aman dalam mengatasi lesi prakanker serviks pada program "See and Treat".*

[Maj Obstet Ginekol Indones 2016; 4-4: 227-233]

***Kata kunci**: Indonesia, inspeksi visual asetat (IVA), krioterapi, see and treat*

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INTRODUCTION

Cervical cancer still becomes the main health problem in the world. World Health Organization (WHO) in 2012 stated that this disease ranked the fourth most prevalent cancer among women. Approximately 528,000 new cases are detected each year, 85% of which are found in developing countries. From those cases, 266,000 cases die, where 9 of 10 death cases occur in developing countries.[1] In 2011, Cancer Registry Council of Pathology Specialist Association in Indonesia stated that this disease was the second most prevalent cancer in women with the incidence rate of 3,047 (12.27%).[2]

Cervical cancer has higher rate of incidence in developing countries compared with developed ones. Furthermore, patients suffering from cervical cancer in developing countries are often diagnosed at advanced stage of diseases so that the 5-year survival rate is less than 40%.[3] Actually, the disease requires 10-20 years to transform from pre-cancer lesions to cancer and whenever it reaches the advanced stage, the survival rate drops significantly. Compared with its first stage, the second, third, and fourth stage have an estimated hazard ratio of 3.09, 18.11, and 53.03; respectively.[4,5]

Structured screening program for cervical cancer is responsible for decreasing the incidence and mortality rate of cervical cancer in developed countries. In United States, the incidence of cervical cancer had dropped by 70% for the last 50 years.[6] Unfortunately, in the developing countries, the screening is not distributed equally and the

coverage is still low. Only 5% of the population has access to the screening program. Apart from that, the health care service is not comprehensive and holistic causing the high prevalence of cervical cancer. This problem also includes of low awareness of the disease among the population. As the population grows, there will be an increase number of cervical cancer patients.[7,8]

World Health Organization analyzed that in the developing countries, screening program using Pap smear cannot significantly decrease the incidence and mortality rate of cervical cancer. Limited budget, low competent resources, and inadequate health care system contribute to the failure of Pap smear screening in those countries.[9] Visual inspection with acetic acid (VIA) is known as the alternative effective method in detecting precancerous lesion in the developing countries. It is both sensitive (67-92.3%) and specific (49-99.8%).[10,11] Therefore, VIA is considered as one of the most popular screening method for precancer lesion, especially in low-resource health care facility.[12]

The management of precancerous lesion involves cryotherapy, loop electrosurgical excision procedure (LEEP), laser, and knife conization.[5] However, the limitation of the resource makes screening methods is not feasibly perform. Therefore, to handle this problem, Indonesia has "See and Treat" program, namely screening using VIA and management through cryotherapy.[13] The effectivity of cryotherapy in treating the precan-cerous lesion ranges from 81.4% to 96.4% for cervical intraepithelial lesion (CIN) I and from 68% to 82.1% for CIN II-III.[14-17] The complaint after cryo-therapy procedure is around 5.6%, including minimal bleeding (1.3%). There is no major complication reported after cryotherapy.[15,18]

In Indonesia, the evaluation of IVA after cryotherapy in "See and Treat" program had been done between 2004 and 2006; the effectivity reached 92%.[16] However, data about the effectiveness of cryotherapy in Indonesia after 2006 was still limited. Therefore, this study aims to describe the VIA result after cryotherapy in "See and Treat" program in Indonesia.

METHODS

We used descriptive cross-sectional study design using medical records from 2010 to 2015. We recruited by total sampling method. "See and treat" program was a single-visit approach program implemented at the low-resource primary health care in Indonesia. It aimed to diagnose the cervix precancerous lesion through VIA and treat positive VIA result with cryotherapy in Indonesia. The evaluation of VIA conversion was performed 6 months after cryotherapy. Every patient's data was written on the medical record.

Participants

We included all women who had positive result of VIA, had received the cryotherapy as treatment; then they visited to control in 6 months after cryotherapy and we could track the complete medical records in primary health care. We categorized lost-to-follow-up for subjects who could not be recalled due to inactive number or unavailable contact. Therefore, we excluded those criteria.

Procedure

History taking and physical examination were performed by the general practitioner in primary health care to exclude the cervicitis, nabothian cyst, and polyp. We detected the cervical precancerous lesion by using a 5% diluted acetic acid solution. The result of VIA was inspected visually with adequate light source. It was considered positive result if there were acetowhite lesions on the transitional zone close to the squamocolumnar junction. When the VIA result was positive, cryotherapy become the choice of treatment in this program. Cryotherapy using cryoprobe was provided in two cycles, with 3 minutes of freeze and 5 minutes of thaw in each cycle. After the process, we prescribed the analgesic and a dose of antibiotic. We also informed the side effects of cryotherapy and instruction not to have sexual intercourse for a month. The patient was informed to come for follow-up session in a month and six months afterwards. The one-month follow-up after cryotherapy aimed to assess the side effect of cryotherapy, such as severe abdominal cramp, fever more than 38°C, or bloody and purulent discharge. The six-month follow-up after cryotherapy would like to assess the conversion of VIA. Patients had the conversion of VIA if the VIA result became negative on six-month follow-up. Failure of cryotherapy was divided into failure to achieve VIA conversion and suspected invasive cancer. Further follow-up was done to observe the cause of cryotherapy failure. We took the data from the medical record; thus, we had to contact the subject in every missing data.

Calculation and data management

Data were analyzed univariately by separating the conversion of VIA on the six-month follow-up into three groups, namely successful conversion, failure to convert, and suspected invasive cancer. We analyzed the data through Microsoft Excel.

RESULTS

From 2010 to 2015, there were 143 medical records which showed the positive VIA result. Fifty-seven (39.86%) data were excluded because 8 of them (5.59%) did not do the cryotherapy and the rest of them (49 data) were lost to follow-up. Four data (2.80%) were dropped out due to missing data. Therefore, there were only 86 (57.34%) data continuing to analyze.

Demographic Characteristics

Of 86 medical records, most of the subjects were 30-39 years old (40.7%) with the first-marriage age of 20-24 years old (52.3%), having 1 to 3 children, and never smoke (98.84%). The number of subjects using hormonal and non-hormonal contraceptive were similar (33.72% vs 29.07%).

Table 1. Characteristics of Subjects

Variables	n	%	Median (min-max)
Age (years old)			35.0 (19.0-57.0)
<20	1	1.2	
20-29	18	20.9	
30-39	35	40.7	
40-49	28	32.6	
50-59	4	4.7	
First-marriage age (years old)			23.0 (16.0-33.0)
<20	16	18.6	
20-24	45	52.3	
25-29	19	22.1	
30-34	6	7.0	
History of contraceptive usage			
None	20	23.26	
Pill	15	17.44	
Intrauterine device (IUD)	25	29.07	
Injection	14	16.28	
Implant	2	2.32	
Sterile	0	0	
Condom	0	0	
Combination	10	11.63	
Number of marriage (times)			
1	85	98.84	
2	1	1.16	
Parity			
0	5	5.81	
1	27	31.40	
2	26	30.23	
3	21	24.42	
4	6	6.98	
5	1	1.16	
Smoking			
No	85	98.84	
Yes	1	1.16	

The VIA Result Six Months after Cryotherapy

"See and Treat" program required the patients to do the repeated VIA test on the six months after cryotherapy to assess the conversion of VIA result. There were 90.70% cases of VIA positive cases converting to negative; while, the rest of the cases did not show the conversion. None of the cases were progress to become the invasive cancer (Table 2).

Table 2. VIA Result Six Months after Cryotherapy

	n	%
IVA -	78	90.70
IVA +	8	9.30
Suspicious of invasive cancer	0	0
Total	86	100

DISCUSSION

"See and Treat" program aims to detect and treat the cervical cancer from its precancerous lesion at the low resource setting of primary health care center.[13] This is a single visit approach program that using VIA to screen and cryotherapy to treat whether the result is positive. This program can decrease the lifetime risk of cervical cancer from 35-year-old women who have not been screened on her entire life.[16]

The implementation of "See and Treat" program involves four pillar: Firstly, the training of VIA and cryotherapy; secondly, improving the awareness of the society; thirdly, detection and treatment using VIA and cryotherapy; the last one is referral system activation when obtaining a difficult case that has a high progressivity to cervical cancer.[13,16] The focus of this study is on the third point which aims to evaluate the VIA conversion after six-month of cryotherapy.

After six-month of cryotherapy, the conversion rate of VIA reached 90.7%. Similar study by Vet JNI, et al. in Jakarta, Tasikmalaya, and Bali from 2007 to 2010 also showed the similar result, namely 92.0%.[19] While it seemed that there was a drop on the successful conversion rate of 1.3%, the difference in this proportion did not differ statistically. It was due to the high prevalence of loss to follow-up and/or incomplete data (37.07% in this study VS 52.60% in the Vet JNI, et al study).[19] The target of "See and Treat" conversion rate was still not available. Looking to the number of successful cryotherapy which reached 90.7%; thus, the cryotherapy could be reliable to convert the VIA result.

Subjects that failed having VIA conversion to negative were 30-49-year old (75.0%) group with the first-marriage age of 20-24 years old (87.5%), history of one marriage (100%), having 2 children (50%), and non-smoker. According to the theory, those results were similar to the risk factors of cervical cancer. Aziz MF in 2009 through their study stated that younger first-marriage age (less than 20 years old) had 8 times risk to be cervical cancer.[20] Pramita S in 2010 concluded that number of parity was also related to the cervical cancer (OR=2.59; 95% CI 1.02-6.61).[21] In addition, smoking could also increase the risk of squamous cell carcinoma (RR 1.50; 95% CI 1.35-1.66).[22,23] Number of marriage in this study was not suitable to the theory stated that the behaviour of changing partners increased the incidence of cervical cancer up to 4 times.[20] However, the number of marriages cannot represent the behaviour of changing partner.

Based on the history of contraception, 75% of the subjects who used injection contraceptive failed to achieve the VIA conversion; while, the other 25% were using pills as the method of contraceptive. That result was similar to the theory that more than five year consumption of oral contraceptive contributed to 1.9 times risk for cervical cancer.[21] We did not count the risk of that although contraception is one of the risk factors for the VIA conversion. Although the cryotherapy success rate in "See and Treat" program reached 90.7%, there were 8 people (9.3%) who did not show the VIA conversion to negative. Those patients were then referred to Dr. Cipto Mangunkusumo Hospital (RSCM) as the national referral hospital in Indonesia for the further definitive diagnosis and management. The failure of VIA conversion can be caused by several factors, such as equipment, healthcare provider, VIA false-positive, and referral system factor.

Looking to equipment factor, problems that could be happened came from the cessation and leaking of gas flow.[24] Brief survey from the healthcare providers in this study showed that the cryoprobe could sometimes stop automatically before ending the two cycles of cryotherapy. Unfortunately, no further information was reviewed and analyzed in this study.

Judging from the healthcare provider factor, problems, such as technical method error, untrained healthcare provider doing the cryotherapy, and lack of update the new methods became the burden for the program's success rate because of failure for the ablation of the cervical precancerous lesion. Observation of the cryotherapy process was performed to evaluate the technique practiced by the primary healthcare provider. Examining from the method, the healthcare providers had used the same method of cryotherapy as what the guideline recommended including 2-cycle cryotherapy with 3 minutes of freezing and 5 minutes of thawing per cycle. The healthcare providers were considered expert in their job as they had done this job for at least 5 years.

In terms of VIA examination, false positive was a common interpretation. The right history taking and interpretation of VIA were necessary to prevent over diagnosis and overtreatment of the cervical precancerous lesion. Observing the process of VIA examination, the supervisor did not confirm the diagnosis. Therefore, the failure of VIA conversion could also be caused by missed diagnosis. In the primary healthcare facilities, the referral of patients to RSCM was a good decision to exclude the possibility of false positive diagnosis.

Another problem was related to the implementation of national healthcare coverage Jaminan Kesehatan Nasional (JKN). In JKN era, the referral system follows the level of health care. Therefore, patients from the primary health care cannot be referred directly to RSCM. This problem was occurred on one patient, whereas, she could not be examined the colposcopy examination due to unavailable tools in the secondary health care. However, the difference of protocol in that hospital contributed to the unsuccessful colposcopy referral.

Ideally, every failure of VIA conversion after cryotherapy should be referred to RSCM to be evaluated in the "See and Treat" program by Female Cancer Program. However, tiered referral system hampered this process. Therefore, recommended advice was either inviting regional doctors to participate in this program or modifying the rules of the referral system to suit this program.

Other problems could also be seen from the side of the primary healthcare. We got 6 loss to follow-up subjects; thus, it made a confusion for the false positive result. Meanwhile, tracking through phone number or home address was difficult due to the lack of identity data recorded in primary health care.

Taking into consideration of those aspects, the failure of VIA conversion in "See and Treat" program could be caused by lack of cryoprobe quality to ablate the precancerous lesion; lack of referral knowledge to ensure the definitive diagnosis as soon as the conversion failure was known; the complicated referral system held in Indonesia contributing to the delayed colposcopy for definitive diagnosis; no policy for primary health care workers to follow-up post referral patients; lack of knowledge equalization about referral system for colposcopy among regional public hospitals.

While failure of VIA conversion was detected, we did not find the progressing lesion to cervical cancer. Therefore, VIA and cryotherapy technique in "See and Treat" program was considered effective in screening and early treatment for the cervical precancerous lesion cases.

We also evaluated the timing of control after cryotherapy. While this study and Vet JNI, et al considered the first and sixth month after cryotherapy as the suitable control time, WHO recommended that the control should be done a year after cryotherapy. The consideration of the first-month control was to evaluate the side effects of cryotherapy; while, the consideration of the sixth-month control was to evaluate the VIA conversion. The cut-off of 6 months was considered as the novelty of this program in Indonesia. Prompt evaluation of the cases was expected to be able to minimize the incidence of cervical cancer progressivity. Two studies having been conducted in Indonesia proved the constancy of VIA conversion in this program.

The number of loss to follow-up in Indonesia was still high. Therefore, the system of patients' identity registry, such as patients' telephone number and the system of reminding patients, such as by contacting the patients at the time of control should be considered.

In terms of side effects, the side effect due to cryotherapy was only happened on one subject. We could state that cryotherapy was safe enough. This result was supported by Blumenthal, et al., Vet JNI, et al., and Fong J, et al. as their studies showed the similar result.[16,18,25] However, they did not

mention the proportion of side effect occurrence in post cryotherapy patients. Sankaranarayanan R, et al. observed that the side effects and complications of cryotherapy were happened only in a small proportion of the population and they were not life-threatening.[14] Therefore, cryotherapy was a safe treatment method for precancerous lesion. However, there were still no studies that focused on side effects of cryotherapy. Therefore, further studies should be held to evaluate the degree of safety from cryotherapy.

CONCLUSION

More than 90% (90.7%) women showing VIA-positive have VIA conversion after 6 months of cryotherapy. We do not find the progression to invasive cancer in 6 months. Therefore, cryotherapy in this program is effective in the early management cervical precancerous lesion.

RECOMMENDATION

Some recommendations for the next study consist of the need to evaluate "See and Treat" program from other aspects to further increasing the coverage rate; the need of further assessment about the aetiology of VIA-conversion failure, such as the false-positive of VIA result, the quality of cryoprobe, the competency of user, and the impact of referral system nowadays in contributing to the barrier of making definitive diagnosis; the regional doctors should be included in implementing this program in regional general hospital or the rules of tiered referral system of JKN should be modified to suit this program; the recommendation of a-year control after cryotherapy as mentioned by WHO can be implemented in Indonesia; the need of patients' information registry to remind patients to control the VIA conversion.

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