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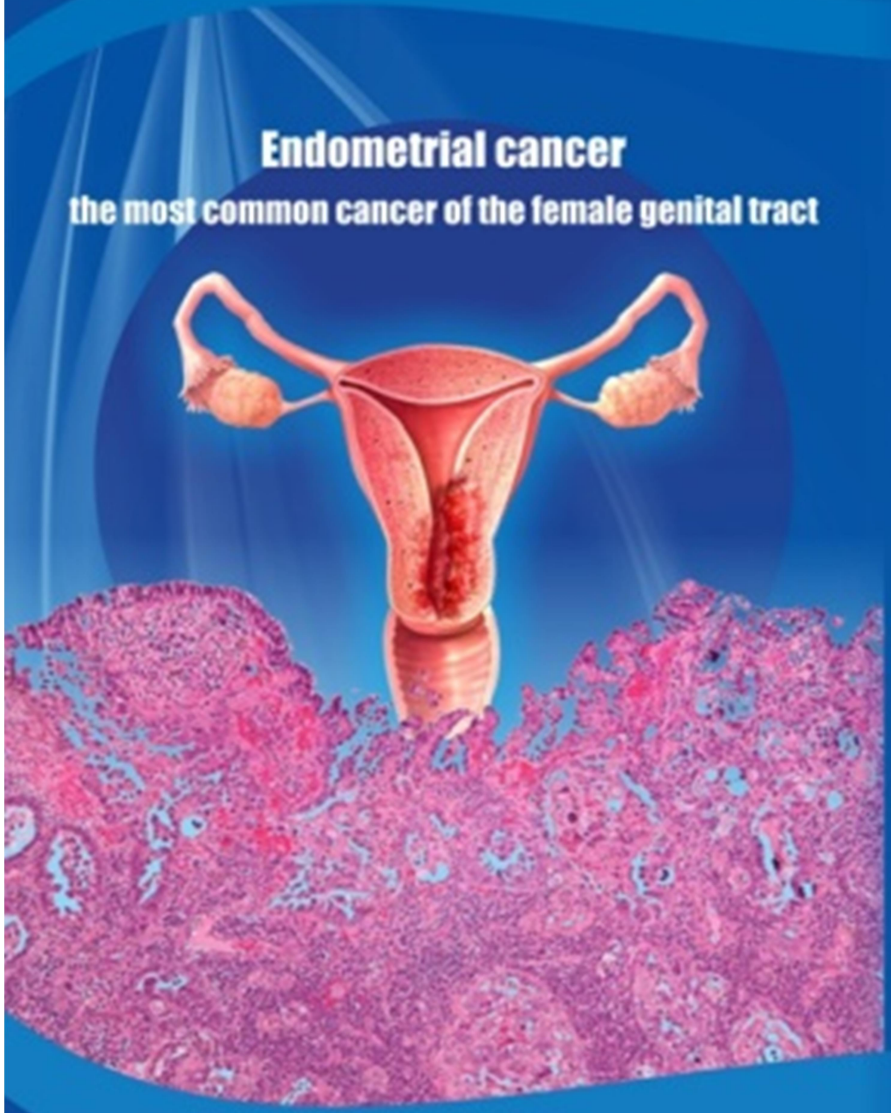

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RESEARCH ARTICLE

Editorial

The Role of Gynecologists in Managing Endometrial Cancer

Sigit Purbadi

Endometrial cancer is the most common female cancer in developed countries.[1]In Indonesia, cervical cancer is the fourth most common cancer after cervical cancer, ovarian cancer and malignant trophoblastic disease.* Geographic condition and limited number of gynecologic oncologists are associated with patients access in oncologic services.

Can gynecologist manage endometrial cancer? This is a common question from patients because there are many cases of inadequate treatment for endometrial cancer. Gynecologists should be competent enough to diagnose endometrial cancer to guide treatment for the patients properly. Finally, gynecologists should be competent to treat endometrial cancer in selective patients.

Base on histopathology, endometrial cancer divided into two types. Type 1 is related to unopposed estrogen, and the histopathology is endometrioid adenocarcinoma. This type generally is low-grade. Type II is mostly high-grade or has histopathology as papillary serous adenocarcinoma or clear cell carcinoma. This grouping is crucial because the gynecologist only allowed to manage the low-risk group; it means the histopathology must be type I and clinically stage 1A. The reason why gynecologist did not have any competency to manage type II endometrial cancer because surgical management is different; its surgical staging included pelvic and paraaortic lymphadenectomy. This competency was not stated in the curriculum.

How to diagnose endometrial cancer? The procedure can be started from clinical and imaging examination to evaluate the tumour mass, including the invasiveness of endometrial cancer. This invasiveness can be determined by using ultrasonography examination, computed tomography scan and magnetic resonance imaging.[2] The golden standard for diagnosingendometrial cancer ishistopathological examination. The specimen for histopathology could be taken from endometrial biopsy or curettage. Biopsy-guided hysteroscopy is an optional procedure in endometrial cancer in Indonesia. However, it is recommended in the United States of America.[2-4] One critical point is that gynaecologist must be competent to diagnose endometrial cancer based on histopathological examination as type 1 and from an image is stage 1A, because only stage 1A endometrial cancer stage and well-differentiated endometrioid adenocarcinoma are allowed to betreated by gynecologists. The management includes fertility-sparing procedure or other surgical procedures. These competencies are stated in the curriculum of Obstetrics and Gynecology speciality program education. The clue of fertility-sparing management in endometrial cancer should be based on the basic concept of endometrial cell proliferation and cell cycle arrest. Several hormones which have anti-proliferation is a modality for fertility-sparing management.[4-6]Surgical management for low-risk endometrial cancer can be managed by hysterectomy with or without bilateral salpingo-oophorectomy. Therefore, every education centre must train obstetrics and gynecology residents adequately. The Indonesian Obstetrics and Gynecology College is responsible for making this policy, including quality control in this process of training, which is this point stated in the logbook. Hopefully, for the next decade, endometrial cancer will be managedadequately.

*Indonesia Pathology Base Cancer Report 2015

REFERENCES

1. Clinical SGO, Endometrial P, Working C, Burke WM, Orr J, Leitao M, et al. Gynecologic Oncology Endometrial cancer : A review and current management strategies : Part II. Gynecol Oncol [Internet]. 2014;134(2):393–402. Available from: http://dx.doi.org/10.1016/j.ygyno.2014.06.003
2. Braun MM, Army M, Overbeek-wager WEA, Army E, Hospital C, Carson F, et al. Diagnosis and Management of Endometrial Cancer. Am Fam Physician. 2016; 93(6):468-74.
3. Clinical SGO, Endometrial P, Working C, Burke WM, Orr J, Leitao M, et al. Gynecologic Oncology Endometrial cancer : A review and current management strategies : Part I. Gynecol Oncol [Internet]. 2014;134(2):385–92. Available from: http://dx.doi.org/10.1016/j.ygyno.2014.05.018
4. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol. 2015;117(3):559–81.
5. Lu KH. Management of Early-Stage Endometrial Cancer. 2009;36(2):137–44.
6. Tock S, Jadoul P, Squifflet J, Marbaix E. Fertility Sparing Treatment in Patients With Early Stage Endometrial Cancer, Using a Combination of Surgery and GnRH Agonist : A Monocentric Retrospective Study and Review of the Literature. 2018;5:1–10.

Research Article

Evaluation of the Accuracy of Implementation of Obstetric Referral Cases to the Emergency in the Jaminan Kesehatan Nasional (JKN) Era

Evaluasi Ketepatan Pelaksanaan Rujukan Kasus Gawat Darurat Obstetri ke Instalasi Gawat Darurat dalam Era Jaminan Kesehatan Nasional

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Abstract

Objective : To investigate the circumstances of the obstetric referral case at the emergency department of the Dr.Cipto Mangunkusumo Hospital as well as the accuracy of the referral implementation.

Methods : We used cross-sectional study. Medical records of obstetric patients at Emergency department in RSCM in January 2013-July 2014 were obtained, then information about patients and their characteristic were collected. The accuracy of referral cases is based on emergency obstetric criteria by BPJS rules.

Results : Primary Health Care became the leading referrer. Inappropriate diagnostic referral cases amounted to 21.2%when JKN first began to be implemented in 2014. Cases with improper diagnoses were more referred when JKN was implemented which amounted to 16.8% and non-emergency referral cases of 6.9% in 2014.

Conclusions : Referral implementation has not been efficient and effective, the number of obstetric referral cases to emergency department of RSCM that can actually be handled in the secondary advanced health services after the application of JKN is still high. Monitoring and evaluation is needed by the Local Health Office to improve the quality of the referral system that applied in the newly JKN era.

Keywords : accuracy of referrals, BPJS, JKN, obstetric emergencies, referral system.

Abstrak

Tujuan : *Mengetahui gambaran kasus rujukan obstetri di IGD RSCM dan ketepatan pelaksanaan rujukan.*

Metode : *Deskriptif desain studi potong lintang. Data diambil dari rekam medis pasien obstetri di IGD RSCM pada bulan Januari 2013 hingga Desember 2014, kemudian informasi mengenai data dan karakteristik pasien dikumpulkan. Ketepatan pelaksanaan rujukan kasus gawat darurat obstetri berdasarkan Krietria gawat darurat bagian kebidanan menurut ketentuan BPJS Kesehatan.*

Hasil : *Perujuk terbanyak adalah Puskesmas (FKTP). Kasus rujukan dengan ketidaksesuaian diagnosis lebih banyak jumlahnya pada saat JKN mulai diterapkan pada tahun 2014 sebesar 21.2%. Kasus dengan diagnosis yang tidak tepat rujuk lebih banyak pada saat JKN di laksanakan yaitu sebesar 16.8% dan kasus rujukan yang bukan gawat darurat sebesar 6.9% pada tahun 2014.*

Kesimpulan : *Pelaksanaan rujukan belum efisien dan efektif, jumlah rujukan obstetri ke IGD RSCM yang sebenarnya dapat ditangani di fasilitas kesehatan tingkat lanjutan sekunder setelah penerapan JKN masih tinggi. Dibutuhkan monitoring dan evaluasi oleh Dinas Kesehatan setempat untuk meningkatkan kualitas sistem rujukan yang berlaku di era JKN yang baru diterapkan.*

Kata kunci : *BPJS, gawat darurat obstetri, JKN, ketepatan rujukan, sistem rujukan.*

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INTRODUCTION

Safe Motherhood is an effort to save women so that their pregnancies and deliveries are healthy and safe, and give birth to healthy babies. The aim of the Safe motherhood effort is to reduce maternal mortality. There are 4 strategic pillars that support this program, namely Family Planning, Antenatal Care, Clean and safe delivery, and Essential Obstetrics Services.[1-3] Health financing is one of the main factors in improving general health services and specifically maternal and child health services.[4-8]

It is realized that limited funding is a big threat in achieving optimal health status. Health financing resources need to be explored more from existing sources in the community and directed to be more rational and efficient to improve service quality. This situation encourages the need for a strategic

step in creating a holistic financing system that is often known as the Community Health Care Guarantee (CHCG). The important thing in health financing is how to use these costs effectively and efficiently from economic and social aspects and can be enjoyed by all people in need. The application of health financing with the insurance system will shift individual responsibility to group responsibility.[9,10]

Every pregnancy contains risks, therefore, every pregnant woman must have access to obstetric emergency services. To avoid the occurrence of ongoing complications, good and appropriate management is needed, which is supported by a good referral system. This referral system is structured in stages, starting with primary care with doctors, secondary services with specialist doctors, and tertiary services with sub-specialist doctors.[11,12]

With the enactment of the Jaminan Kesehatan Nasional program, it is necessary to evaluate the program whether the implementation of obstetric referrals is appropriate in accordance with the provisions of the BPJS, especially the obstetric referral cases to RSUPN Dr. Cipto Mangunkusumo as a national hospital, this can be used as an evaluation and consideration in health system policies.

METHODS

A cross sectional descriptive design was conducted for this study which illustrates the accuracy of obstetric referral cases to the Dr. Cipto Mangunkusumo Hospital RSCM IGD in 2013 and 2014 based on the diagnosis of obstetric emergencies according to the BPJS rule, before and during the National Health Insurance Program organized by BPJS. The inclusion criteria in this study were obstetric referral cases to RSCM emergency department in year 2013 and 2014. Whereas exclusion criteria include data on obstetric cases that are not referenced, referral case data of patients who died when they arrived at the RSCM Emergency Department before receiving treatment (Death on Arrival). Subjects were taken by total sampling. Calculations were carried out univariate descriptive analysis to find out the distribution and normality. The result is in the form of frequency and percentage (proportion) which presented in the form of tables or graphs. Then all analyzes were carried out using SPSS 20.0.

RESULTS

The researcher succeeded in getting the research subjects as many as 5,223 people who were patients referring to obstetric cases at the RSCM Emergency Department throughout year 2013 and year 2014. The year 2013 was the era before JKN, and in 2014 was the JKN era. The number of subjects in year 2013 was 2,251 people, and in year 2014 there were 2,972 people.

To get a description of the pregnancy characteristics of subjects in the era before JKN and JKN era, researchers used several determinants, namely the number of parity, number of gravidas, number of ANC, gestational age, and number of fetuses. From the existing data, it was found that subjects with nullipara parity were the highest number, namely 1,179 people (52.4%) in 2013 and 1,130 people (38.0%) in 2014. In 2013, the number of subjects who had completed the minimum number of ANCs (four times) was 958 people (42.6%), but there were still many who only conducted ANC three times, namely 919 people (40.8%). In 2014, there were more subjects who had successfully completed the minimum number of ANCs, namely 2635 people (88.7%), but those who had never done an ANC had also increased, namely 252 people (8.2%). For gestational age subjects who were referred to the RSCM ED, there were differences in 2013 and 2014. In 2013, the majority of referrals to the RSCM ED were 29-36 weeks with 1.385 people (61.5%). Meanwhile, in 2013, the majority of those referred to the RSCM ED were age> 37 weeks with 2.749 people (92.5%). The highest number of fetuses is a single fetus, with 2.114 (93.9%) in 2013 and 2867 people (96.5%) in 2014.

Tabel 1. Characteristic of Patients in Obstetrics and Gynecology at RSCM ED 2013-2014

Pregnancy characteristics	Number of subject			
	before JKN		at JKN	
	n=2251	%	n=2972	%
Parity				
Nullipara	1,179	52.4	1,130	38.0
Primipara	528	23.5	844	28.4
Multipara	505	22.4	922	31.0
Grande multipara	39	1.7	76	2.6
Gravida 1	1,144	50.8	1,081	36.4
Gravida 2	498	22.1	744	25.0
Gravida 3	399	17.7	797	26.8
Gravida > 3	210	9.3	350	11.8
K1	263	11.7	12	0.4
K2	111	4.9	0	0
K3	919	40.8	73	2.5
K4	958	42.6	2,635	88.7
Never	0	0	252	8.5
Age of pregnancy (weeks)				
< 12	284	12.6	38	1.3
12-28	106	4.7	0	0
29-36	1,385	61.5	185	6.2
> 37	476	21.1	2,749	92.5
Fetus				
Singleton	2,114	93.9	2,867	96.5
Multiple	137	6.1	105	3.5

Primary Health Care remains the most frequent referral to RSCM. Based on its location, in 2013 and 2014 the most referrer were from Central Jakarta with 1105 people (49.1%) and 1155 people (28.9%) respectively

Table 2. Characteristics of Obstetric Patient Referrers at RSCM ED 2013-2014

Referrer Characteristic	Number of subject			
	before JKN		at JKN	
	n=2251	%	n=2972	%
Referrer location origin				
Central Jakarta	1,105	49.1	1.155	38.9
East Jakarta	561	24.9	743	25.0
West Jakarta	114	5.1	185	6.2
South Jakarta	322	14.2	562	18.9
North Jakarta	102	4.5	178	6.0
Other Location	47	2.0	9	4.7
Referrer Type				
Hospital				
Type A	175	7.8	139	4.7
Type B	264	11.7	502	16.9
Type C	28	1.2	28	0.9
Type D	10	0.4	30	1.0
Mother and Child Hospital	8	0.4	2	0.1
Maternity Home	48	46.3	34	1.1
Primary Health Care	1,043	46.3	1,548	52.1
Midwife	604	26.8	651	21.9
Obstetric and Gynecology doctor	43	1.9	34	1.1
GP	28	1.2	4	0.1

The characteristics of the obstetric referral case to the RSCM ED are also sought by the researcher. For this reason, what is examined is the diagnosis of the referrer whether it is correct or not then the reason why the patient is referred, and whether the referral is accompanied by a back-referral letter or not. The results show that most diagnoses are correct, although in 2014 the number of incorrect diagnoses increased. Most of the reasons patients are referred are due to facility problems. While, for a reverse reference letter, no referrer includes a reverse reference letter.

Table 3. Characteristics of Obstetric Referral Cases to RSCM ED 2013-2014

Case Characteristic	Number of subject			
	before JKN		at JKN	
	n=2251	%	n=2972	%
Diagnose				
Appropriate	1,994	88.6	2,317	78.0
Inappropriate	230	10.8	630	21.2
Reason to Referr				
Facility	2,123	94.3	2,815	94.7
Human Resource	56	2.5	52	1.7
Full booked	72	3.2	105	3.5
Reverse Referral request				
Accompanied by referral letter	0	0	0	0
Without reverse referral letter	2,251	100	2,972	100

Table 4. The Accuracy of the Implementation of Referral of Obstetric Cases to the Emergency Department of RSCM

Reference	Number of Subject	
Accuracy	**n**	**%**
Case with correct diagnosis to refer		
Year 2013 (before JKN)	2,019	90.7
Year 2014 (JKN Era)	2,452	83.2
Case with the incorrect diagnosis to refer		
Year 2013 (before JKN)	206	9.3
Year 2014 (JKN Era)	495	16.8

In this study, the results of the accuracy of referral of referral obstetric patients in RSCM IGD in 2013-2014 generally decreased, as many as 2019 cases (90.7%) in year 2013 and 2452 cases (83.2%) in 2014

DISCUSSION

The research subjects were 5223 people who were divided into patients referring obstetric cases at the RSCM IGD in year 2013 and year 2014.

Patient's pregnancy characteristics change with the implementation of the JKN system. The characteristics of the highest number of patient parity in 2013-2014 were nullipara patients, there was a decrease in the percentage of nullipara patients, from 1.144 people (50.8%) to 1081 people (36.4%). This trend continues for obstetric referral patients at the RSCM Emergency Department since 2008 where the value of nullipara patients in 2008 to RSCM was 43.9%. The gestational age of the study subjects experienced a shift from the most gestational age, namely 29-36 weeks for 2013 (61.5%) to more than 37 weeks for 2014 (92.5%).

Furthermore, there was a significant increase in the variable antenatal care visit of patients referring to obstetric cases at the RSCM ED after the implementation of JKN. Previously, the number of patients who had completed the

minimum number of ANCs recommended by WHO four times was only 958 people (42.6%), whereas after the application of JKN, the number had increased to 2,635 people (88.7%). This shows that there are improvements in ANC services after the implementation of the JKN system. This can be caused by reduced barriers to finding health services related to cost issues. However, it was also seen that patients who had never done ANC had also increased to 252 people (8.2%) from none before. This phenomenon shows an effort to look for maternal health services in patients who may have been hindered due to cost problems, because patients who had never done ANC which might be due to limited funds and also increased public knowledge and awareness in understanding maternal emergencies to seek help in competent health facilities.

Based on location, referrals from the Central Jakarta area were still the locations with the most referrers, from as many as 1,105 people (49.1%) to 1,155 people (38.9%), but there was a decrease in percentage along with the increase in the percentage of other referral locations. This illustrates the improvement in the patient's referral system, where in the JKN program, patient referrals are implemented in the first level health services and advanced health facilities regional areas where patients live and the regional referral system runs.

The most health care facilities referring obstetrics and gynecology patients are still primary health centers, from the percentage of 46.3% in year 2013 to 52.1% in year 2014. These figures are accompanied by a decrease in referrals from type A and Mother and Child Hospital RSIA hospitals and an increase in hospital referrals type B significantly indicates an increase in the health referral system when JKN is applied. Primary health care as first level health services should not directly refer to tertiary first level health services but to secondary advanced health services according to the tiered referral pathway implemented by BPJS, but many other factors influence the event, one of which is the request of patients to be referred to certain advanced health services, related to distance, level of trust, availability of facilities, health resources, and certain subspecialties, but this will burden health financing at the tertiary advanced health services level if the case can actually be handled in the secondary advanced health services.

The percentage of diagnoses that are not inappropriate for obstetric case reference patients has increased by almost three fold, from 230 cases (10.8%) in year 2013 to 630 cases (21.2%) in year 2014. While the reason for the highest number of referral patients is still caused for reasons of limited facilities.

During 2013-2014 no referred patients to obstetric cases at the RSCM emergency room accompanied by a back-referral letter. In fact, the obstetric cases that might be handled in primary care after the emergency has been resolved. This shows that there are differences in the ability to diagnose a maternal emergency case at the first level health service and advanced health services levels. Health human resources are certainly needed in providing quality health services, in addition services that are always available with the presence of health workers play an important role in facing maternal emergency cases, such as there is a specialist physician and the availability of emergency operating rooms whenever needed. This phenomenon shows the ineffectiveness and inefficiency of handling referral cases, by burdening health costs and accumulating cases in advanced health serviceswhich should be handled in secondary advanced health services. The accuracy of obstetric referral case in RSCM ED generally decreased significantly. Referral cases with the appropriate diagnosis of referral as much as 90.7% (2,019 cases) in 2013 to 83.2% (2,452 cases) in 2014. These cases should have been resolved at lower levels of health care facilities. A similar phenomenon can also be seen in health centers with other services. For inappropriate referral cases in 2013 there were 206 cases (9.3%) to 495 cases (16.8%) in 2014.

The effectiveness of the maternal referral system can be seen from the indicators of conformance and time. Conformance is the suitability of the reference made, namely by-passing (the reference made is not in accordance with the predetermined stage of reference, namely passing a lower health facility) and non compliance with referral advice (referral that should not be necessary).[13] Where as long as the reference is important to note, whether it is in accordance with the reference path or not. Besides that, it can also be caused by self referrals

(referrals made by pregnant women themselves, where the pregnant women come directly to health facilities at a higher level, without going to low-level health facilities first). The second indicator used is time, this is related to response time for communication (the time needed to communicate with facilities where pregnant women will be referred) and timely treatment of complication (speed in handling complicated cases in referral health facilities).[14-15]Distance factors can also cause obstacles in the referral process, this is because there is an emergency so that the patient or referrer will choose the closest first level health service at that time, this also actually can not be separated from social and cultural factors, the level of trust in certain health facilities.

High-risk or complicating pregnancies are the most cases obtained, which amounted to 1772 cases (78.7%) in 2013 and 2428 cases (81.8%) in 2014. Further more, the second and third most frequent cases of emergency also included abortion (5.3%) and dystocia (4.8%) for 2013 as well as abortion (5.1%) and antepartum bleeding (2.4%) for 2014. Whereas it can be seen a decrease in cases others. Primary health care is the referral facilities with the highest number of false emergencies in 2013 - 2014. This incident caused abuse of maternal health funding in the JKN system, whereas cases that should not be referred to because it is not an emergency case. This can actually be minimized if the role of first level health serviceas a gatekeeper in the national referral system is good.

The number of obstetric referral patients at the RSCM increased after JKN implemented, from as many as 2251 patients in 2013 to 2972 patients in 2014, an increase of 16.5%. This is the opposite of JKN's aim to make the reference level better so that not all patients need to be referred to RSCM as a national referral center hospital. The percentage of type A hospitals as referral health care facilities decreased from 7.4% in 2013 to 4.7% in 2014, while referrals from type D hospitals and health centers increased, each increasing from 0.4% to 1.0 % for type D hospitals and 46.3% for 52.1% for primary health care. This shows more patients who skip the reference level and go directly to the RSCM as type A hospital. After the implementation of JKN there was more diagnosis cases that inappropriate, from 10.8% in 2013 to 21.2% in 2014, more than double the increase in the diagnosis of inappropriate referrals. In addition, there was an increase in cases with an incorrect diagnosis of referral cases from 9.3% in 2013 to 16.8% in 2014.

The data above shows that when the JKN was implemented there was a decrease in the quality of referrals.

CONCLUSION

The number of referral of maternal cases to RSCM IGD in 2013 was 2251 to and in 2014 there were 2972 cases. Of these, none of the referrers included a back-referral letter. This increase in the number of referrals was due to the enactment of the newly implemented JKN program, this was due to the lack of socialization and lack of understanding of the rules in the newly implemented JKN. The Antenatal Care K4 visit on the demographic picture of patients at the time JKN was applied experienced an increase of 958 (42.6%) in 2013 and in 2014 there were 2635 (88.7%). This increased number of visits is due to the reduced barriers to obtaining health services, namely the financing factor where the national insurance system is applied.

The number of appropriate referral cases based on BPJS emergency criteria in 2013 was 90.7% and 2014 was 83.2%. The suitability of the reference diagnosis in 2013 was 88.6% and in 2014 it was 78.1%. The data shows the need for improvement, especially in health human resources and the role of PKM as a gate keeper and increasing the role of secondary advanced health services in the referral system in the JKN program.

Primary health care is the most health facilities that make referrals to RSCM emergency department. The most reason being referred to is due to limited facilities. This indicates a lack of effectiveness and efficiency in referencing maternal cases.

Therefore, continuous socialization should done by BPJS in implementing the JKN rules that have just been implemented by the government, the phenomena that occur are due to the process of adaptation to the new system. Improving the quality of human resources, improving and

improving facilities in first level health service is needed in empowering PKM as a gatekeeper in the JKN system. Better cooperation is needed between health facilities in the success of the JKN program in order to reduce the cost burden and stack of referral cases in advanced health services and abuse health funding. Also routine evaluation is need to perform by policy holders to assess the suitability and accuracy of the referrals to improve the referral system, especially maternal referrals because maternal health reflects the level of welfare of the country.

REFERENCES

1. Jowett M. Safe motherhood interventions in low-income countries: an economic justification and evidence of cost effectiveness. Health Policy. Elsevier; 2000;53(3):201–28.
2. Mahler H. The safe motherhood initiative: a call to action. The Lancet. 1987;1(8534):668-70.
3. Benagiano G, Thomas B. Safe motherhood: The FIGO initiative. Int J Gynecol Obstet. 2003;82(3):263-74
4. Mati K, Adegoke KK, Michael-Asalu A, Salihu HM. Health insurance coverage and access to skilled birth attendance in Togo. Int J Gynecol Obstet. 2018 ;141(2):181–8.
5. Philibert A, Ravit M, Ridde V, Dossa I, Bonnet E, Bedecarrats F, et al. Maternal and neonatal health impact of obstetrical risk insurance scheme in Mauritania: a quasi experimental before-and-after study. Health Pol Plan. 2017;32(3):405–17.
6. Ekman B, Liem NT, Duc HA, Axelson H. Health insurance reform in Vietnam: a review of recent developments and future challenges. Health Policy and Planning. Oxford University Press; 2008 1;23(4):252–63.
7. RI KIDJKKK, 2013. Buku Pegangan Sosialisasi Jaminan Kesehatan Nasional dalam Sistem Jaminan Sosial Nasional [Internet]. Kemenkes RI; 2013:76
8. RI P Peraturan Presiden no 12, tahun 2013,tentang Jaminan Kesehatan Peraturan Presiden 2013.
9. Persada WAJPR, Sistem Kesehatan Nasional. Staff blog ui.ac.id.2007
10. RI P. Undang-undang no 40, tahun 2004, tentang Sistem Jaminan Sosial Nasional. 2004:1-36.
11. Indonesia Menteri Koordinator Bidang Kesejahteraan Rakyat P. Peraturan Pemerintah Republik Indonesia dan Peraturan Presiden Republik Indonesia : sistem jaminan sosial nasional (SJSN) dan Badan Penyelenggaraan Jaminan Sosial (BPJS).2018
12. RI K. PMK No. 001 tentang Sistem Rujukan Pelayanan Kesehatan Perorangan. 2012:1–10.
13. Murray SF, Pearson SC. Maternity referral systems in developing countries: Current knowledge and future research needs. Soc Sci Med. 2006 ;62(9):2205–15.
14. RI K. Sistem Kesehatan Nasional Per Pres 72 tahun 2012. 2013:1–45.
15. Irasanty G, Hasanbasri M, Hakimi M. Efforts to minimize delays in maternal referral in Majene District - Indonesia (Pencegahan Keterlambatan Rujukan Maternal di Majene Indonesia).2008

Research Article

Accuracy of Fetal Weight Estimation Using Hadlock II Formula

Keakuratan Taksiran Berat Janin Menggunakan Rumus Hadlock II

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Abstract

Objective : To investigate the accuracy of estimated fetal weight using Hadlock II formula in RSUD Dr Moewardi.

Methods : This cross-sectional study was conducted at RSUD Dr Moewardi in June 2017. Subjects were women who gave birth at RSUD Dr Moewardi from August 2014 to March 2017. The method of collecting data by quoting the medical record as required. Data analysis was done by using linear regression statistic test.

Results : By distribution, the number of samples that, according to the standard, is 81.67 %. With the value of R = 0.706 which means that the relationship between two research variables are strong and the value of R Square = 0.499 which means that estimated fetal weight using Hadlock II formula has contribution 49.9 % on fetal birth weight and 50.1 % others by other factors.

Conclusions : Fetal weight estimation using Hadlock II formula in RSUD Dr Moewardi has low accuracy. Operator skills training is required to improve the accuracy of estimated fetal weight.

Keywords : fetal birth weight, fetal weight estimation, Hadlock II.

Abstrak

Tujuan : *Mengetahui keakuratan taksiran berat janin menggunakan rumus Hadlock II di RSUD Dr Moewardi.*

Metode : *Penelitian ini adalah penelitian potong lintang. Penelitian ini dilaksanakan di RSUD Dr Moewardi pada Juni 2017. Subjek penelitian ini adalah data rekam medis dari ibu hamil yang mengalami partus di RSUD Dr Moewardi pada Agustus 2014 – Maret 2017. Metode pengumpulan data dengan mengutip data rekam medis pasien sesuai ketentuan. Analisis data dilakukan dengan uji statistik regresi linier.*

Hasil : *Secara distribusi, jumlah sampel yang memenuhi standar yaitu 81,67 %. Dengan nilai R = 0,706 yang artinya bahwa hubungan kedua variabel penelitian ada dalam kategori kuat dan nilai R Square = 0,499 yang berarti taksiran berat janin menggunakan rumus Hadlock II memiliki pengaruh kontribusi sebesar 49,9% terhadap berat bayi lahir sedangkan 50,1 % lainnya dipengaruhi oleh faktor lain.*

Kesimpulan : *Taksiran berat janin menggunakan rumus Hadlock II di RSUD Dr Moewardi kurang akurat. Perlu dilakukan pelatihan ketrampilan operator sehingga diharapkan dapat meningkatkan keakuratan taksiran berat janin.*

Kata kunci : *berat bayi lahir , Hadlock II, , taksiran berat janin.*

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INTRODUCTION

Fetal weight estimation is an essential component for antenatal care, counselling, diagnosis, and delivery. The accuracy of fetal weight estimation is one of the most important measurements at the onset of labor.[1]

Accuracy of fetal weight is an important parameter in predicting neonatal morbidity and mortality and guidelines for determining the next obstetric management.[2] Accurate estimation of fetal weight also has an effect on clinical management, the outcomes of pregnancy, delivery and adaptation of the newborn, especially in cases of macrosomia, delayed fetal growth (PJT), breech presentation, vaginal labour after previous caesarean section.[3,4]

There are two main methods for determining fetal weight estimation, i.e. clinically and using sonography. Clinical estimates are based on abdominal palpation and fundal height.[5] The sonographic estimates are based on Biparietal

Diameter (BPD), Abdominal Circumference (AC), Femur Length (FL) and Head Circumference (HC).

There are many published formulas for calculating fetal weight estimation based on one or more measurements (BPD, HC, AC, FL).[6,7] The most popular formulas are Shepard, Warsof's & Shepard's modifications, and Hadlock's.[8]

Accurate estimation of fetal weight is something that doctors still find difficult to understand.[9] Sonographic estimates are superior to clinical estimates, but require good tools and trained operator.[10]

Estimated fetal weight using ultrasound has the best standard deviation followed by two clinical examinations, Johnson formula and Dare formula.[11] The objective of this study is to investigate the accuracy of fetal weight estimation using Hadlock II formula in RSUD Dr Moewardi.

METHODS

This cross-sectional study was conducted at RSUD Dr Moewardi in June 2017. We reviewed the medical records data of women who gave birth at RSUD Dr Moewardi between the period of August 2014 and March 2017. The sample selection technique used is simple random sampling. The hypothetical tests used were the Kolmogorov-Smirnov test, paired T, and linear regression test. All statistical analyses were performed using SPSS Statistics 23.0 for Windows.

RESULTS

We recruited 52 subjects in total. From this study, there were 63 subjects who met the criteria and 72 subjects who did not meet the inclusion and exclusion criteria for several reasons, 53 subjects were incomplete in biometric measurements, 2 subjects of Intra Uterine Fetal Death (IUFD), 9 subjects oligo / polyhydramnios, 5 subjects with gestational age <37 weeks, and 3 subjects with anatomical, congenital and chromosomal abnormalities. From 63 subjects who met these criteria, 60 subjects were selected in a simple random sampling by the researcher. The results obtained from this study are.

Table 1. Description of the Subjects

Variable	n	Mean (grams)	Standard Deviation
EFW using Hadlock II formula	60	2997.06	± 321.411
Birth weight	60	2986.67	± 357.234

EFW: Estimated Fetal Weight
N: Number of subjects

Based on the data in table 1, the average estimated fetal weight with Hadlock II formula of 60 subjects was 2997.06 grams while the average of weight babies born from 60 subjects was 2986.67 grams.

From the results of the study, the mean difference between the estimated fetal weight using Hadlock II formula with a birth weight of 60 subjects was 206.41 ± 159.85 gram or 7.02 ± 5.67%. The highest difference of fetal weight estimation using Hadlock II formula with birth weight in RSUD Dr Moewardi was 776.35 gram or 31.05% and lowest was 2.20 gram or 0.08%.

Table 2. Distribution of Subjects Differences

Characteristic	n	Mean (grams)	Standard Deviation
Weight (grams)			
< 300	49	136.72	±75.00
> 300	14	452.69	±141.44
Percentage (%)			
< 10	50	5.06	±3.51
> 10	13	15.46	±5.88

N: Number of subjects

Table 2 showed that there were 48 subjects with the difference less than 300 grams and 12 subjects with the difference of more than 300 grams. In the percentage of the difference estimated fetal weight using Hadlock II formula with the birth weight, 49 subjects had a difference less than 10% and 11 subjects with the difference more than 10%.

There was no significant difference between fetal weight estimation using Hadlock II formula and the birth weight ($p = 0.76$). In linear regression test obtained SPSS calculation results with the value of $R = 0.706$, which can be interpreted

that the relationship between the two research variables are in a strong category. In addition, the results of R Square = 0.499, which means the estimation fetal weight using Hadlock II formula has a contribution influence of 49.9% on birth weight and other 50.1% influenced by other factors beyond the estimation fetal weight using the formula Hadlock II.

DISCUSSION

From this study, it was found that there was no significant difference between the fetal weight estimation using the Hadlock II formula with the birth weight. This is in line with the research was conducted that explained that the fetal weight estimation using the Hadlock II formula was not more different from the birth weight of the baby because the formula using three biometric parameters in the measurement, Biparietal Diameter (BPD), Abdominal Circumference (AC), and Femur Length (FL)[12].

Factors that affect the size of the difference between the fetal weight estimation using the formula Hadlock II with the birth weight of 60 subjects studies were various, such as the formula used, operator skills, ultrasound, pregnancy conditions, and others.[4,11,13] Table 2 showed the distribution of difference between the fetal weight estimation using Hadlock II formula and the birth weight of 60 subjects. In the table, 48 subjects or 80% of the subjects were met the standard because the results were ≤ 300 grams.[8] When viewed from the percentage, the difference between the fetal weight estimation using Hadlock II formula and the birth weight, there were 49 subjects or 81.67% who met the standard because they had the difference less than 10%.[14] It means, in distribution, fetal weight estimation using the Hadlock II formula in RSUD Dr Moewardi is less accurate because of the number of samples that meet the standard (the difference between fetal weight estimation using Hadlock II formula and birth weight ≤ 300 gram or ≤10%) is 81.67%. While the standard of accuracy of fetal weight estimation using Hadlock II formula is 93%.[8]

Based on paired T-test obtained Sig. value ie p = 0.760, it means that there is no significant difference between the fetal weight estimation using the Hadlock II formula and the birth weight, this is in accordance with described that the result of the fetal weight estimation using the Hadlock II formula were not more different from birth weight[11]. While on the linear regression test obtained value of R = 0.706, it means that the relationship between two research variables are in a strong category.[7] In addition, obtained the value of R Square = 0.499, which means that estimation fetal weight using Hadlock II formula has a contribution influence of 49.9 % to the birth weight and other 50.1% is influenced by other factors beyond the estimation fetal weight using the Hadlock II formula.

The accuracy of fetal weight estimation in RSUD Dr Moewardi is not only influenced by the formula that used to calculate the fetal weight estimation. Other factors such as operator skills, ultrasonography and pregnancy may also affect the accuracy of fetal weight estimation.[9,13] This is supported by the results of this study that R Square = 0.499, which means that fetal weight estimation using Hadlock II formula has an influence contribution of 49.9% to the birth weight and another 50.1% is influenced by other factors beyond the fetal weight estimation using the Hadlock II formula.

CONCLUSION

Fetal weight estimation using Hadlock II formula in RSUD Dr. Moewardi is less accurate, because the distribution of the samples that meet the standard (the difference of fetal weight estimation using Hadlock II formula with birth weight ie ≤300 gram or ≤10%) is 81.67%, less than 93%.[8] From the results of the study, it can be concluded that the fetal weight estimation using Hadlock II formula in Dr Moewardi Hospital is overestimated or greater than baby birth weight. In addition, the fetal weight estimation using the Hadlock II formula in RSUD Dr. Moewardi has an influence on the birth weight of 49.9%, while the other 50.1% is influenced by other factors.

REFERENCES

1. Njoku C, Emechebe C, Odusolu P, Abeshi S, Chukwu C, Ekabua J. Determination of Accuracy of Fetal Weight Using Ultrasound and Clinical Fetal Weight Estimatios in Calabar South, South Nigeria. Int Scholarly Research Notices 2014 ; 2014 : 1-2
2. Schmidt U, Temerinac D, Bildstein K, Tuschy B, Mayer J, Sutterlin M, et al. Finding The Most Accurate Method to Measure Head Circumference for Fetal Weight Estimation. Eur J Obstet Gynecol Reprod Biol 2014 ; 178 : 153-6.
3. Melamed N, Ben-Haroush A, Meizner I, Mashiach R, Yogev Y, Pardo J. Accuracy of Sonographic Fetal Weight Estimation : A Matter of Presentation. Ultrasound Obstet Gynecol 2011 ; 38 : 418–24
4. Huber C, Zdanowicz JA, Mueller M, Surbek D. Factors Influencing The Accuracy of Fetal Weight Estimation with A Focus on Preterm Birth at The Limit of Viability : A Systematic Literature Review. Fetal Diagnos Therapy 2014 : 1–8
5. Sharma N, Srinivasan J, Sagayaraj MB, Lal DV. Foetal Weight Estimation Methods – Clinical, Sonographic and MRI Imaging. Int J Scien Research Publications 2014 ; 4(1) : 2
6. Shittu AS, Kuti O, Orji EO, Makinde NO, Ogunniyi SO, Ayoola OO, et al. Clinical Versus Sonographic Estimation of Foetal Weight in Southwest Nigeria. J Health Popul Nutr 2007 ; 25(1) : 14-23
7. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic Estimation of Fetal Weight. The Value of Femur Length in Addition to Head and Abdomen Measurements. Radiol 1986 ; 150(2):535-40
8. Kumara DMA, Perera H. Evaluation of Six Commonly Used Formulae for Sonographic Estimation of Fetal Weight in a Sri Lankan Population. Sri Lanka J Obstet Gynecol 2009; 31 : 20-33.
9. Annapurna K, Rama Ch, Ramamani C . A Comparative Study of Fetal Weight Estimation at Term by Clinical Method and Ultrasound Method and After Delivery. Ind J Applied Research 2015 ; 6 (5) : 118-23.
10. Gerard GN, Harold S. Ultrasonographic Prediction of Term Birth Weight: How Accurate is It?. Am J Obstet Gynecol 2003 ; 188(2) : 566-74
11. Kumari A, Goswami S, Mukherjee P. Comparative Study of Various Methods of Fetal Weight Estimation in Term Pregnancy. J South Asian Feder Obstet Gynecol 2013 ; 5(1) : 22-5
12. Mattsson N, Rosendahl H, Luukkaala T. Good Accuracy of Ultrasound Estimations of Fetal Weight Performed by Midwives. Acta Obstreticia Gynecologica 2007 ; 86 : 688-92
13. Pinto A, Pinto F, Faggian A. Sources of Error in Emergency Ultrasonography. Critical ultrasound 2013 : 1-5
14. Abele H, Hoopmann M, Wagner N, Hahn M, Wallwiener D dan Kagan KO. Accuracy of Sonographic Fetal Weight Estimation of Fetuses with A Birth Weight of 1500 g or Less. Eur J Obstet Gynecol Reprod Biol 2010 ; 153(2): 131–7

Research Article

Oxytocin 10 IU as Prophylactic for Uterine Atony : a Randomized Clinical Trial

Oksitosin 10 IU sebagai Profilaksis Atonia Uteri : suatu Uji Coba Klinis Acak

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Abstract

Objective : To compare the effectiveness of oxytocin dose of 10 IU and 20 IU for preventing uterine atony in women undergoing cesarean section.

Methods : This was a double-blind, randomized clinical trial with good matching selection with randomization block of patients who had risk factors for the occurrence of uterine atony such as preeclampsia, patients were receiving MgSO4, oxytocin intrapartum and chorioamnionitis who performed stratified randomization prospectively with two kinds of oxytocin doses which are 10 IU and 20 IU as a prophylaxis for uterine atony in women who performed emergency cesarean section with transverse incision and were using a general anesthesia.

Results : This study found no any significant differences between the use of 10 IU and 20 IU as prophylaxis for uterine atony during cesarean section either in its action at the time or while in recovery room, especially on the cases without chorioamnionitis thus using oxytocin 10 IU regimen can be considered, besides the effectiveness did no differ, it will cost cheaper than oxytocin 20 IU regimen which frequently used.

Conclusions : There were no significant differences in the incidence of blood loss during the cesarean section between the treatment of oxytocin 10 IU group and oxytocin 20 IU group. The additional uterotonic was using during the action of the cesarean section between the treatment of oxytocin 10 IU group, and oxytocin 20 IU group gave no significant differences. The side effects in this study at least form of chills and vomiting found no significant differences between both of groups despite the side effects that arise in oxytocin 20 IU group was higher at 23.08% than oxytocin 10 IU group at 15.19%. Chorioamnionitis would be a risk factor for the occurrence of uterine atony during the action of the cesarean section if it associated with the use of additional uterotonic in oxytocin 10 IU group if compared with oxytocin 20 IU group.

Keywords : cesarean section, oxytocin, uterine atony.

Abstrak

Tujuan : *Untuk membandingkan efektifitas penggunaan dosis 10 IU dan 20 IU sebagai profilaksis atonia uteri pada saat seksio sesarea.*

Metode : *Penelitian ini menggunakan uji klinis acak ganda dengan seleksi yang sesuai dengan blok acak pada pasien-pasien yang memiliki faktor risiko terjadinya atonia uteri seperti preeklamsia, pasien yang diberikana MgSO4 dan oxytocin intrapartum sebelumnya serta chorioamnionitis yang dilakukan pengacakan secara prosfektif bertingkat yang diberikan dua jenis dosis oksitosin yaitu 10 IU dan 20 IU sebagai profilaksis atonia uteri pada perempuan yang dilakukan seksio sesarea darurat dengan insisi transversal dan menggunakan anestesi umum.*

Hasil : *Penelitian ini menemukan tidak adanya perbedaan yang bermakna antara penggunaan dosis oksitosin 10 IU dan 20 IU sebagai profilaksis atonia uteri pada seksio sesarea baik saat tindakan operasi maupun saat berada di ruang pemulihan, terutama pada kasus-kasus tanpa khorioamnionitis dimana memerlukan oksitosin tambahan pada kelompok 10 IU, selain efektifitasnya tidak berbeda, akan lebih murah dari pada rejimen oksitosin 20 IU yang sering digunakan saat ini.*

Kesimpulan : *Berdasarkan hasil penelitian ini, tidak ada perbedaan yang bermakna dalam kejadian kehilangan darah selama operasi seksio sesarea antara perlakuan kelompok oksitosin 10 IU dan kelompok oksitosin 20 IU. Penggunaan uterotonik tambahan selama tindakan seksio sesarea antara perlakuan kelompok oksitosin 10 IU dan kelompok oksitosin 20 IU tidak memberikan perbedaan yang signifikan. Efek samping dalam penelitian ini yakni menggigil dan muntah, tidak ditemukan perbedaan yang bermakna antara kedua kelompok meskipun efek samping yang muncul pada kelompok oksitosin 20 IU lebih tinggi 23,08% dibandingkan kelompok oksitosin 10 IU pada 15,19%. Khorioamnionitis merupakan faktor risiko terjadinya atonia uteri selama tindakan seksio sesarea jika dikaitkan dengan penggunaan uterotonika tambahan pada kelompok oksitosin 10 IU jika dibandingkan dengan kelompok oksitosin 20 IU.*

Kata kunci : *atonia uteri, oksitosin, seksio sesarea.*

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INTRODUCTION

The labour is a culmination point of the human reproduction process by women after pregnancy over the course of time and a certain period. Postpartum haemorrhage is one of the leading causes of morbidity and mortality in mothers. In Indonesia, the causes of maternal death of mothers are haemorrhage (67%), infection (8%), toxaemia gravidarum (7%) and abortus (10%).[1-3] The cases of postpartum haemorrhage were mostly caused by uterine atony, which is about 50 – 60% that can be prevented. The General Hospital Central Palembang, reported since 1986–1989 of 12.476 deliveries with 67 maternal deaths are cases of haemorrhage 36,6% with 10% of them are caused by uterine atony.[3]

The postpartum haemorrhage is most often defined as a state of blood loss from 500 mL – 600 mL in vaginal delivery during the first 24 hours after birth and 1000 mL at delivery by cesarean section. Various risk factors have a significance, by itself and by the combination that causing the bleeding postpartum, which are placenta previa, placental abruption, twin pregnancy, weight of birth is 4000 g or more, obesity, the kind of anesthesia that used, induction of labour, gave birth with an action, infection and obstacles in the progress of labour. Besides the vaginal laceration, the cause of bleeding commonly found is hypotonic myometrium.[3-6]

The existence of uterine atony has been thought would increase the postpartum haemorrhage. The uterine atony is a significant contribution to the occurrence of blood loss, especially after the action of cesarean section.[4-5] Oxytocin has been widely used to prevent the uterine atony after childbirth.,[7-12] The use of oxytocin, during the action of cesarean section to prevent uterine atony, is mostly based on experiences and only focus on vaginal delivery regimen guidance.

This study is meant to compare the effectiveness of oxytocin dose of 10 IU and 20 IU as prophylactic uterine atony in cesarean section. Comparing the incidences of bleeding that occurs, changes of hemoglobin level, hematocrit level and hemodynamic function and determine the use of additional uterotonic after treatment on both of oxytocin groups, to know the side effects that arise and identify the risk factors of uterine atony in the action of cesarean section against both of those oxytocin groups.

METHODS

This study was conducted with mothers that decided to deliver with an emergency transperitoneal cesarean section. Subjects were women with 22 weeks of pregnancy or more who went into labour.

Clinical Examination Methods

This study was using double-blind, randomized clinical trial with good matching selection with 6 randomization block of patients who had risk factors for the occurrence of uterine atony such as preeclampsia, patients were receiving MgSO4, oxytocin intrapartum and chorioamnionitis who performed stratified randomization prospectively with two kinds of oxytocin doses which are 10 IU and 20 IU as prophylactic of uterine atony in women who underwent emergency transperitoneal cesarean section.

Laboratory Examination Methods

Measurement of haemoglobin concentration, hematocrit and leukocyte in units of g% for haemoglobin, vol% for hematocrit and mm3 for leukocyte with machine Cauter Mode DTH2 AS. Manufactured by Cauter Corporation. Avenue, Miami. USA.

Data Analyst

The variables studied were oxytocin 10 IU and 20 IU , age, parity, birth weight, an indication of cesarean section, the amount of bleeding, the use of additional uterotonics (oxytocin, methyl ergotamine, misoprostol), duration of operating time, side effects, blood transfusions, blood pressure, pulse, temperature, hemoglobin and hematocrit level, the use of MgSO4, oxytocin intrapartum, clinical chorioamnionitis, duration of membrane rupture.

RESULT

Based on the statistical analysis, there were no differences in mean age in both groups ($\rho > 0.05$).

Table 1. Characteristic of the Subjects

Characteristic	Oxytocin 10IU n%		Oxytocin 20IU n%		Mean ± SD
Age (years old)	29.39 ± 6.17		29.45 ± 5.74		29.42 ± 5.938*
Education					
No School/not completed elementary	7	8.9	8	10.3	
Elementary School	25	31.6	26	33.3	
Junior High School	15	19.0	21	26.9	
Senior High School	19	24.1	13	16.7	
Academy	9	11.4	3	3.8	
University	4	5.1	7	9.0	
Occupation					
No Job	41	51.9	43	54.8	
Labor	2	2.5	4	2.5	
Farmer	8	10.1	7	9.6	
Trader	7	8.9	8	9.6	
Private Employees	9	11.4	4	8.3	
Government Employes	12	15.2	12	15.3	
Address					
City	52	33.1	50	31.8	
Countryside	27	17.2	28	17.8	
Gestational Age					
Gestational Age (weeks)	39.14 ± 1.95		38.96 ± 1.57		0.242
Baby's Birth Weight					
Birth Weight (g)	3199.36 ± 586.48		3093.04 ± 623.56		0.335

Table 2. Characteristic Period, Blood Loss, Haemoglobin and Hematocrit Level

Characteristic	Oxytocin 10 IU	Oxytocin 20 IU	mean ± SD
Period of the action of cesarean			
Duration of action (minutes)	57.512 ± 5.5777	58.0506 ± 6.6850	0.184
Blood loss (mL)	475.51 ± 219.73	556.35 ± 330.37	0.56
The mean and the difference of haemoglobin level and hematocrit level			
Haemoglobin before cesarean section	10		.876 ± 1.389 10.631 ± 1.541 0.599
Haemoglobin after 24 hours	9		.737 ± 1.275 9.582 ± 1.345 0.746
Differences in haemoglobin level	1		.054 ± 1.052 1.136 ± 0.988 0.298
Hematocrit before cesarean section		33.40 ± 4,87	0.532
Hematocrit after 24 hour	33.53 ± 4,580	30.17 ± 4.22	
Differences in haematocrit level	30,14 ± 4,030 3.28 ± 3.14	3.35 ± 3.58	

In this study, the mean gestational age was 39.62 ± 0.948 weeks with the average age at oxytocin 10 IU group was 39.14 ± 1.95 weeks, and at oxytocin 20 IU group was 38.96 ± 1.57 weeks ($p > 0.05$). The youngest gestation was 28 weeks, and the oldest gestation was 43 weeks.

The mean of birth weight babies as a superficial mother that did the action of cesarean section in both of the groups was 3145.86 ± 605.926 g. The lightest birth weight of babies was 1600 g, and the heaviest was 4800 g. In this study showed no significant differences of the mean of superficial birth weight of babies when the action of the cesarean section had done neither in oxytocin 10 IU3199.36 ± 586.48 g nor oxytocin 20 IU 3093.04 ± 623.56 g ($\rho > 0.05$).

Table 3. The Characteristics of Reproductive, Intrapartum, Indication C-section and Additional Uterotonic, Side Effect and Risk Factors.

Characteristic	Oxytocin 10 U (%)	Oxytocin 20 U* (%)	*P-value* (%)
Reproductive Status			
Nullipara	31 (39.7)	27 (34.2)	58 (36.9)
Multipara	43 (55.1)	49 (62.0)	92 (58.6)
Grandemultipara	4 (5.1)	3 (3.8)	7 (4.5)
Intrapartum Characteristics			
$MgSO_4$ Intrapartum Oxytocin	14 (17.7)	11 (14.1)	0.664
Without Oxytocin	60 (75.9)	55 (70,5)	0.589
Induction	2 (2.5)	5 (6,4)	0.276
Acceleration	17 (21.5)	18 (23.1)	0.702
Chorioamnitis	7 (8.9)	8 (10.3)	0.793
Another Median of Rupture Membrane	268.99 ± 455.37	300.90 ± 545.65	0.277
Others	5 (6.3)	4 (5.1)	9 (5.7)
Indication C-section			
CPD/FPD	15 (19.0)	12 (15.4)	27 (17.2)
Fetal distress	8 (10.1)	10 (12.8)	18 (11.5)
Transverse lie	4 (5.1)	8 (10.3)	12(7.6)
Neglected labour	32 (40.5)	26 (33.3)	58 (36.9)
Haemorhage antepartum	15 (19.0)	18 (23.1)	33 (21.0)
Others	5 (6.3)	4 (5.1)	9 (5.7)
The Use of Additional Uterotonic			
Additional uterotonics	34 (21.70)	29 (18.50)	0.279
Oxytocin	28 (35.44)	22 (28.51)	0.351
Metilergometrin	7 (4.50)	10 (6.40)	0.453
Misoprostol	-	-	-
Side Effects			
Chills	8 (5.01)	13 (8.03)	0.250
Vomiting	4 (2.05)	5 (3.02)	0.746
Total	12 (15.19)	18 (23.08)	
Risk Factors			
Neglected labour	11 (47.80)	12 (52.20)	0.260
$MgSO_4$ intrapartum	7 (63.60)	4 (36.40)	0.930
Oxytocin intrapartum	19 (45.24)	23 (54.76)	0.278
Chorioamnionitis	8 (88.90)	1 (11.10)	0.001

*Chi Square Oxytocin 20 U : Þ>0.05

The mean of blood loss between both of treatment groups found no significant differences, where oxytocin 10 IU group had 475.51 ± 219.73 mL, and oxytocin 20 IU group had 556.35 ± 330.37 mL (ρ> 0.05) with the mean of blood loss between both of the groups were 515.67 ± 282.24 mL.

The mean of haemoglobin level before the action of cesarean section was 10.754 ± 1.4669 g% with the lowest level about 5.5 g% and the highest level 15.7 g%, while the mean of hematocrit level was 33.46 ± 4.714 vol% with the lowest level of about 19 vol% and the highest level about 48 vol%.

In this study, the mean of haemoglobin level before the action of cesarean level, as well as 24 hours after the action, found no significant differences (ρ> 0.05) with the difference in oxytocin 10 IU group was 1,054 ± 1.052 g%, and the mean of haemoglobin level was 0.820 ± 1.288 g%. In the oxytocin 20 IU group, the differences were 1.136 ± 0.988 g% with the mean of haemoglobin level 0.912 ± 1.361 g%. The differences of hematocrit level in oxytocin 10 IU was 3,28 ± 3,14 vol% with the mean of hematocrit level 2.58 ± 3.97 vol% and in oxytocin 20 IU was 3.35 ± 3.58 vol% with the mean of hematocrit level 2.54 ± 4.15 vol%.

The number of parity in this study varied from respondents who have never given birth before (nullipara), multipara: 1-5 times and grandmultipara: 6 times or more. The results found no significant difference in mean parity of each group, which is 1.37 ± 1.85 times on oxytocin 10 IU group and 1.53 ± 1.75 times on oxytocin 20 IU group (ρ> 0.05).

The characteristic of intrapartum between both treatment groups was similar, that was

the patient who received $MgSO_4$, oxytocin, the incident of chorioamnionitis and the duration of the membrane to be ruptured. This study found no significant differences in intrapartum characteristics between both treatment groups (ρ> 0.05).

The most indication for the action of cesarean section was neglected labor 58 cases (36.9%) with 32 cases (40.5%) at oxytocin 10 IU group and 26 cases (33.3%) at oxytocin 20 IU group that was meant statistically found no significant differences between both of treated groups (ρ = 0.877). Generally, statistical analysis found no significant differences between both of the groups against the indication of cesarean section (ρ> 0.05).

Oxytocin is the preparation that often used as an additional uterotonics in this study, about 28 cases (35.44%) for oxytocin 10 IU and 22 cases (28.21%) for oxytocin 20 IU, followed by addition of methergine about 7 cases (4.5%) compared to 10 cases (6.4%) in each treatment groups. From statistically analysis found no significant differences between both treatment groups against the use of additional uterotonics (ρ> 0.05).

The use of additional uterotonics during the action of cesarean section is an action that given by an operator to avoid the uterine atony on patients in action so that the more of blood loss could be prevented because the operator could immediately assess and diagnose the contraction from uterine.

This results showed that both of the groups were needed additional uterotonics, so that found no significant differences in both of them (ρ = 0.260). In cases that were used $MgSO_4$ intrapartum, from 25 cases about 11 cases of it (44%) need additional uterotonics with details, 7 cases (63.6%) got additional uterotonics in oxytocin 10 IU group and 4 cases (36.4%) in oxytocin 20 IU group. The result of statistical analysis showed that $MgSO_4$ intrapartum is not the significant risk factor for uterine atony could happen (ρ = 0.93).

Like wise the cases that got oxytocin intrapartum, either induction or acceleration, where from 42 cases that got oxytocin intrapartum, about 19 cases (45.24%) with 17 cases (89.47%) of it accelerated at oxytocin 10 IU group and 23 cases (54.76%) with 18 cases (78.26%) of it accelerated at oxytocin 20 IU. It found no significant differences in risk factors for uterine atony on the cases that got oxytocin while intrapartum in both of treatment groups (ρ = 0.278), that means, in fact, the both of treatment groups almost the same, they require an additional uterotonic.

The interesting in this study, the cases with clinical chorioamnionitis diagnosis that got treatment of oxytocin 10 IU had significant risk factors for occurrences the uterine atony, about 16 cases with chorioamnionitis, 8 cases (88.9%) in oxytocin 10 IU and 1 case (11.1%) in oxytocin 20 IU(ρ = 0.001).

The changes of haemodynamics status assessed were: the changes of blood pressure systolic and diastolic, pulse, temperature and the changes in oxygen saturation before and after the action of the cesarean section. From statistical analysis found no significant differences between the mean of haemodynamics status of respondents in both treatment groups both before and after the action of cesarean section (ρ> 0.05).

The side effects observed were allergy, diarrhoea, hypotension, chills, vomiting and others that might be caused by the use of oxytocin. In detail, the side effects that arose both treatment groups can be seen in the table below.

This study seems to reinforce the use of oxytocin preparation to prevent uterine atony in postpartum especially in the action of cesarean section, that commonly used in many countries because it is a safe drug and has no side effects on the heart if administered intravenously and continuously.

DISCUSSION

Based on the statistical analysis, found no significant differences on the mean of age, that was 29.42 ± 5.938 years old in both of the treatment groups, in oxytocin 10 IU as well as oxytocin 20 IU (ρ> 0.05). Munn MB et al reported a mean of age of 25 ± 6 years old for low doses

of oxytocin 10 IU group and 25 ± 6 years old for high doses of oxytocin 80 U, meanwhile in who compared prostaglandin $F_{2\alpha}$with oxytocin 20 IU got the mean of age was about 29.2 ± 5.9 years old for prostaglandin and 30.5 ± 3.8 years old for oxytocin group. Both studies showed that they had no significant differences in the mean of ages; this result is the same as the result of this study.[12,13]

The number of parity in this study varied from respondents who never give birth (nullipara), multipara: 1 – 5 times and grand multipara: 6 times or more. A number of parity counted based on the history of labour ever experienced at gestational age above 22 weeks.[2] In this study the mean of parity in both of the treatment groups was 1.45 ± 1.795 times with range 0 to 9 with the reproductive status of respondents mostly was multipara about 92 cases (58.6%) with 43 cases (55.1%) on oxytocin 10 IU group and 49 cases (62%) on oxytocin 20 IU group. This study found no significant differences at the mean of parity in each group, that was about 1,37 ± 1,85 times on oxytocin 10 IU group and 1.53 ± 1.75 times on oxytocin 20 IU group (ρ> 0,05). The result had no differ much compared to results that obtained by Dansereau et al, who compared carbetocin (1,2 ± 0,8) with Oxytocin (1,2 ± 0,9) in the action of cesarean section.[10]

The mean of gestational age was 39.62 ± 0.948 weeks, in oxytocin 10 IU group was about 39.14 ± 1.95 weeks, and in oxytocin 20 IU was about 38.96 ± 1.57 weeks. The youngest gestational age was 28 weeks, and the oldest was 43 weeks. From the result, the mean of gestational age between both treatment groups found no significant differences (ρ> 0.05). The gestational age was 37 ± 4.3 weeks in oxytocin with low doses group and 37 ± 4.9 weeks in high doses group, while got the result that did not much difference in this study, that was 38.4 ± 0.9 weeks in oxytocin 20 IU group and the comparison group was 38.5 ± 0.8 weeks.[12]

The mean birth weight babies as superficial of mothers that had an action of cesarean section in both of the groups were 3145.86 ± 605.926 g. In this study showed no significant differences of the mean of superficial birth weight babies in action of cesarean section are performed, either in oxytocin 10 IU group was about 3199,36 ± 586,48 g or in oxytocin 20 IU group was 3093.04 ± 623.56 g (ρ> 0.05). The mean birth weight babies were 3284 ± 367 g for oxytocin 20 IU group and about 3139 ± 461 g for $PGF_{2\alpha}$ group.[12]

The mean of cesarean section duration was about 57.7834 ± 6.1460 minutes, treatment with dose oxytocin 10 IU group 57.51228 ± 5.5777 minutes and oxytocin 20 IU group 58.0506 ± 6,6850 minutes, with the range time of cesarean section between 45 to 75 minutes. From the statistical analysis found no significant differences between both of the treatment groups in duration of action (ρ> 0,05). This duration is less with the mean of duration of action for each treatment groups was similar, that was 52 ± 16 minutes on low dose and 54 ± 18 minutes on high dose(ρ = 0.53) and got the mean was about 45,1 minutes in 20 IU group and 47.5 minutes in the comparison groups.[12,13]

The indication to perform an emergency action of cesarean section include DKP or FPD, fetal distress, HAP (placenta previa and placental abruption), neglected labour and abnormalities position of babies as well as other indications such as a history of cesarean section twice as much as 8 cases, each treatment group were 4 cases and six years of primary infertility was 1 case in oxytocin 10 IU group. The indications that the most took an action of cesarean section were neglected labour about 58 cases (36.9%) with 32 cases (40.5%) in oxytocin 10 IU group and 26 cases (33.3%) in the oxytocin 20 IU group, which means in statistical analysis found no significant differences between both treatment groups (ρ = 0,877). The result was the same as that obtained where the most indication of cesarean section caused by neglected labor, was 41% for oxytocin with low dose and 34% for another (ρ = 0,16) and different with the result that obtained where the most indication was the former of cesarean section about 66.67% in oxytocin 20 IU group and 50% in the comparison group.[12,13]

The Intrapartum characteristics of both treatment groups are almost the same. No significant differences for intrapartum characteristics between both treatment groups (ρ> 0.05). This result was the same, but this study did not have amnioinfusion characteristics as they had obtained as 19% for a low dose of oxytocin and 23% for high dose because this procedure

was not the routine procedure that held in this department.[13]

The mean of blood loss between both treatment groups found no significant differences, with the mean of blood loss between both of the groups was 515.67 ± 282.24 mL(ρ> 0.05). This result was the same although the mean of bleeding between both of treatment groups in this study was less than they have obtained, that was about 957 ± 148 mL in oxytocin with a low dose and 937 ± 159 mL (ρ = 0.08). The haemoglobin and hematocrit level was the critical variable to assess the blood loss in this study. In this study, obtained the mean of haemoglobin level before the action of cesarean section was 10.754 ± 1.4669 g% with the lowest 5.5 g% and the highest 15.7 g%, while the mean of hematocrit level was 33.46 ± 4.714 vol%, with the lowest was 19 vol% and the highest was 48 vol%. In this study, the mean of haemoglobin level before the action of cesarean section and 24 hours after the action of cesarean section showed no significant differences (ρ> 0.05).

Haemoglobin and hematocrit level in statistically had no significant differences showed that the influence of haemoglobin and hematocrit level as a causal factor to success and failure in preventing of bleeding in the cesarean section could be ignored in both of the groups in this study. In this study, the mean of blood loss and decreasing hematocrit level found no differences between both treatment groups. It was predicted because uterine atony is easily diagnosed and treated at the time the action of the cesarean section took place because the uterus was exposed and more easily evaluated than vaginal deliveries. This situation will facilitate the introduction, and prompt treatment with the use of additional uterotonic thus would reduce the blood loss more.

Reduction, the amount of blood loss during the action of the cesarean section, was beneficial for patients that could reduce morbidity and the need for blood transfusion after the action. Although an accurate determination of blood loss required at the time of surgery, it was very challenging to do, especially inaction of the cesarean section because of the influence of the amniotic fluid and meconium. Blood loss less than 500 mL during the action of the caesarean section could still be considered the accurate, but if more of it would be difficult to estimate the blood loss.[10]This study realized the difficulties, but the double-blind, randomized clinical trial has reduced bias in assessing blood loss and this study also compared the change in haemoglobin and hematocrit level.

Oxytocin is a preparation that is often used as an additional uterotonic in this study, based on the statistical analysis found no significant difference between both of the treatment groups against the use of additional uterotonic (ρ> 0.05). These results differ from previous studies obtained which is as much as 39% in small doses of oxytocin 10 IU versus 19% on large doses of 80 U (ρ<0.01, RR 2.1 95% CI, .4, 3).[13]

More widespread use of oxytocin as an additional uterotonic in this study, when compared to other types of uterotonic, seems to correspond with the function of oxytocin as first-line preparation to prevent postpartum haemorrhage. The absence of the addition of misoprostol during surgery, this might be related to the way of this preparation was less practical during the action of the cesarean section. There were 4 cases the addition of methergine as a second line of uterotonic after adding oxytocin to prevent the persistent uterine atony. There was no discontinuation solution case study because of complications during the action of the cesarean section. More on this study, obtained in recovering rooms the additional uterotoniceach oxytocin 10 IU group: methergine. These results indicated that the need for additional uterotonic in recovering room between both treatment groups was not much different. In this study, changes in hemodynamic status were assessed include changes in systolic and diastolic blood pressure, pulse, temperature and the changes in oxygen saturation before and after cesarean section. From a statistical analysis showed no significant difference between the mean haemodynamic status of respondents between both treatment groups before and after the action of cesarean section (ρ> 0.05).

Obtained the minimal side effects, so there was no termination solution for the study due to side effects. Hypotension and water intoxication were often feared the clinicians due to the use of oxytocin in this study was not found. There

were no significant differences between the side effects that arise (chills and vomiting) in both of treatment groups (ρ> 0.05), although the incidence of adverse events was slightly higher in the group of 20 IU (23.08%) compared to the group of 10 IU (15.19%). From this research seems to reinforce the use of preparations of oxytocin to prevent postpartum uterine atony at cesarean section, especially when the action that has been widely used in many countries as it is a safe drug and has no side effects on the heart when administered intravenously and continuously. This drug has been recommended in various studies and writings with its use as an isotonic solution simultaneously antidiuretic effect and the possibility of hyponatremia.

In this study, patients who experience such disruption labour progress were required the additional uterotonic at oxytocin 10 IU group (47.8%) and in oxytocin 20 IU group (52.2%). The results indicate both of groups is almost the same that was needadditional uterotonic preparation so that there were no significant differences between both treatment groups (ρ = 0,260). These results differ from the study those obtained in which the ratio of 41% was obtained at 10 IU oxytocin group and 22% in the comparison group (ρ = 0,001). In cases with the use of intrapartum $MgSO_4$, 44,00% of them required an additional uterotonic atoxytocin 10 IU group (63,60%) and the oxytocin 20 IU group (36.40%). From the statistical analysis, it turned MgSO4intrapartumwas not a significant risk factor for the occurrence of uterine atony, (ρ = 0,93). These results were the same as those obtained which was 32% versus 29% (ρ = 0,57).[13]

Likewise with cases that got intrapartum oxytocin, either induction or acceleration. There were no significant differences in risk factors for the occurrence of uterine atony in cases that got oxytocin when intrapartum in both of treatment groups (ρ = 0.278) in the sense that almost the same both of treatment groups required additional uterotonic. The interesting thing about this study, it turns out the cases with a diagnosis of clinical chorioamnionitis who received treatment oxytocin 10 IU proved to have a significant risk factor for the occurrence of uterine atony, as much as 88.9% and 11.1% in the group treated with oxytocin 20 IU (ρ = 0.001). These results were obtained from studies in which a low dose of 10 IU treatment was more need for additional uterotonic in emergency action of cesarean section when compared with high-dose oxytocin (50% versus 24% with ρ> 0.001).[13]

CONCLUSION

Referring to the results of this study, which is not found significant differences between the use of oxytocin 10 IU and 20 IU as prophylactic of uterine atony on the actions of cesarean section either at the time the action caesarean section as well as in the recovery room, especially in cases without chorioamnionitis, then the use of regimen oxytocin 10 IU could be considered, in addition to its effectiveness did not differ, the cost of which will be paid half cheaper when compared to the regimen of 20 IU which has been frequently used. The results of this study ultimately expected to be a recommendation on the use of oxytocin as prophylaxis of uterine atony during cesarean section in obstetric practice every day.

The use of uterotonic preparations should still be used to prevent uterine atony and reduced bleeding duringcesarean section. Oxytocin regimen of 10 IU can be considered to be the first line as prophylaxis for uterine atony during cesarean section, especially in those without chorioamnionitis.

REFERENCES

1. Arias F. Practical guide to high-risk pregnancy and delivery. 2nd ed. St. Louis: Mosby Year Book Ins 1993; 433-41.
2. Saifuddin AB, Andrianz G, Wiknjosastro GH, Waspodo D. Buku acuan nasional pelayanan kesehatan maternal dan neonatal. Ed Pertama. Jakarta: JNPKR-POGI-Yayasan Bina Pustaka Sarwono Prawirohardjo 1995;3-9:100-21.
3. Chalik TMA. Hemoragi utama obstetri dan ginekologi. Jakarta: Widya Medika 1987;160-88.
4. Bukowski R, Hankins GDV. Managing postpartum hemorrhage. Contemp Obstet Gynecol 2001; 92-101.
5. Singla AK, Berkowitz RL, Saphier CJ. Obstetric hemorrhage in Jehovah's Witnesses. Contemp Obstet Gynecol 2002;4:32-43.
6. Leveno KJ, Cuningham FG, Gant NF, et al. Williams manual of obstetrics. 21st ed. New York: McGraw-Hill 2003;377-9.
7. Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. Br Med J 1988; 297:1295-1300.
8. Adashek JA, Peaceman AM, Zeno JAL, Minogue JP, Socol ML. Factors contributing to the increased cesarean birth rate in older parturient women. Am J Obstet Gynecol 1993; 169:936-40.

9. Pangemanan WT dkk. Kecenderungan seksio sesar di RSUP Palembang (1987-1989). Makalah KOGI VIII. Palembang: Bagian/SMF Obstetri dan Ginekologi FK Unsri/RSUP 1990.
10. Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER et all. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol 1999; 180:670-6.
11. Winkler CL, Gray SE, Hauth JC, Owen JO, Tucker JM. Mid-second-trimester labor induction: concentrated oxytocin compared with prostaglandin E2 vaginal suppositories. Obstet Gynecol 1991; 77:297-300.
12. Chou MM, MacKenzie IZ. A prospective, double-blind, randomized comparison of prophylactic intramyometrial 15-methyl prostaglandin $F_{2\alpha}$, 125 microns, and intravenous oxytocin, 20 IU nits, for the control of blood loss at elective cesarean section. Am J Obstet Gynecol 1994; 171:1356-60.
13. Munn MB, Owen J, Vincent R, Wakefield M, Chestnut DH, Hauth JC. Comparison of two oxytocin regimens to prevent uterine atony at cesarean delivery: a randomized controlled trial. Obstet Gynecol 2001; 98:386-90.

Research Article

The Risk of Sensorineural Hearing Impairment in Preeclampsia

Risiko Gangguan Pendengaran Sensorineural pada Pasien Preeklamsia

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Abstract

Objective : To determine the risk of sensorineural hearing impairment in preeclampsia patients and to in Obstetric and Gynecology Department in Dr. Mohammad Hoesin Hospital Palembang.

Methods : An analytic observational case-control study was held in Dr. Mohammad Hoesin Hospital Palembang from 1st January to 31st December 2016. Subjects were obtained through consecutive sampling. Hypothetical tests used were unpaired t-test, Chi-square test and Fisher test for expected deviation standard <5, significance determined based on p-value if p<0.05. Data progressing and analysis were done using SPSS version 17.0 for windows.

Results : Characteristics distribution of the subjects were overall homogenous. With the Chi-square test, no significant difference was found in hearing function examination with OAE and tympanometry in both groups (p>0.05). From unpaired t-test, there was no significant difference between mean Air Conducting (AC) and Bone Conducting (BC) of the right ear in severe preeclampsia group and healthy pregnancy group (p=0.340), as well as mean AC and BC of the left ear in severe preeclampsia group and healthy pregnancy group (p=0.059). Based on the Fisher's Exact test, no significant relation was found between severe preeclampsia and sensorineural hearing impairment (p=0.999).

Conclusions : There was no significant relation between severe preeclampsia and sensorineural hearing impairment in Obstetric and Gynecology Department in Dr. Mohammad Hoesin Palembang.

Keywords : otoacoustic emission, preeclampsia, sensorineural hearing impairment.

Abstrak

Tujuan : *Mengetahui risiko gangguan pendengaran sensorineural pada pasien dengan preeklamsia di Departemen Obstetri dan Ginekologi RSUP Mohammad Hoesin Palembang.*

Metode : *Penelitian analitik observasional dengan disain kasus kontrol pada wanita hamil di RSMH sejak 1 Januari – 31 Desember 2016. Subjek dipilih secara pengambilan sampel berturut - turut. Analisis dengan uji t tak berpasangan, Chi-square, dan uji Fisher untuk ekspektasi sd<5, kemaknaan ditentukan berdasarkan (p) jika p<0.05. Proses mengolah dan analisis data ini dilakukan menggunakan SPSS 17.0 for windows.*

Hasil : *Distribusi karakteristik umum subjek secara keseluruhan adalah homogen. Berdasarkan uji Chi Square, tidak didapatkan perbedaan bermakna hasil pemeriksaan fungsi pendengaran dengan OAE dan Timpanometri pada kedua kelompok (p>0,05). Dengan uji T tidak berpasangan, tidak didapatkan perbedaan bermakna rerata Air Conducting (AC) dan Bone Conducting (BC) telinga kanan kelompok PEB dan kelompok hamil normal (p=0,340), begitu juga dengan rerata Air Conducting (AC) dan Bone Conducting (BC) telinga kiri kelompok PEB dan kelompok hamil normal (p=0,059). Berdasarkan uji statistik Fisher, tidak didapatkan hubungan bermakna antara preeklamsia berat dengan gangguan pendengaran sensorineural (p=0,999).*

Kesimpulan : *Tidak terdapat hubungan yang bermakna antara preeklamsia berat dengan gangguan pendengaran sensorineural berdasarkan pemeriksaan audiometri di Departemen Obstetrik dan Ginekologi RSUP Dr. Mohammad Hoesin Palembang.*

Kata kunci : *gangguan pendengaran sensorineural, otoacoustic emission, preeklamsia*

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INTRODUCTION

Hypertension in pregnancy is a group of disorders including gestational hypertension, preeclampsia, eclampsia, chronic hypertension, and superimposed preeclampsia on chronic hypertension. Preeclampsia and eclampsia affect 2-8% pregnancies worldwide and are the leading cause of maternal mortality due to hypertensive disorder in pregnancy.[1,2]

A study showed resistance to ultrastructural change in arterial subendothelium in women with preeclampsia. Decreased blood flow causes distribution disorder and tissue ischemia that leads to necrosis, bleeding, and other organs disorder. This systemic disorder in preeclampsia may also affect hearing ability.[3]

This research is aimed to determine the risk of sensorineural hearing impairment in women with preeclampsia and to compare otoacoustic emissions appearance between women with severe preeclampsia and normotensive women.

METHOD

This analytic observational case-control study was held from 1st January to 31st December 2017 in Obstetrics and Gynecology Department of Dr. Mohammad Hoesin Hospital Palembang/Medical Faculty of Universitas Sriwijaya Palembang.

A sample of 50 women who fulfilled the inclusion criteria was obtained. Inclusion criteria include women with severe preeclampsia in Dr. Mohammad Hoesin Hospital Palembang, who was pregnant with single live fetus, and agreed to join the study and has signed an informed consent form. Exclusion criteria in this study are women with a history of hearing impairment; history of ear, nose, or throat surgery that may affect hearing ability; had upper respiratory tract diseases, acute otitis media, or otitis media with effusion at the time of examination; who consumed ototoxic drugs; were older than 40 years old; and women with obesity, heart disease, diabetes mellitus, chronic hypertension, kidney disease, and endocrine disorders.

Data was collected by measuring blood pressure, body weight, and body height; checking for the presence of proteinuria and other laboratory abnormalities through laboratory examinations, and performing the hearing test in pregnant women with severe preeclampsia in Dr. Mohammad Hoesin Hospital Palembang. Blood pressure was measured twice in lying down position. Hearing test was performed with tympanometry and Transient Evoked Otoacoustic Emission at frequency 1000, 1500, 2000, 3000, and 4000.

Data analysis was done with unpaired t-test, Chi-square test, and Fisher test using SPSS version 17.0 for windows.

RESULT

A sample of 50 women who fulfilled inclusion criteria was divided into severe preeclampsia group (n=25; 50%) and normotensive group (n = 25; 50%).

In the severe preeclampsia group, 84% of women were within the age group of 20-35 years old with mean age 28.68 ± 5.77 years old. Similarly, in the normotensive group, 96% of women were within the age group of 20-35 years old with a mean age of 27.12 ± 4.09 years old. Full-term gestational age (≥ 37 weeks gestation) in both groups were 68% in severe preeclampsia group and 100% in normotensive group. Preterm pregnancies were found in 32% severe preeclampsia group with the youngest gestation of 23 weeks gestation. Distribution of gravidity characteristic in both groups was similar, both with 64% multiparous and 36% primiparous. Distribution of general characteristics of study subjects is homogenous.

Statistical analysis showed no significant difference in hearing function test with OAE and tympanometry in both groups was found ($p > 0.05$). The result of the hearing function test with OAE and tympanometry was shown in table1.

Audiometry evaluation showed the mean value of right ear Air Conducting (AC) and Bone Conducting (BC) was 19,69 ± 3,18 dB in severe preeclampsia group and 20,43 ± 2,19 dB in the normotensive group. With unpaired t-test, no significant difference was found between these two groups ($p=0.340$). Similarly, audiometry of the left ear showed mean values of AC dan BC in severe preeclampsia group was 19,40 ± 3,80 dB

and 19,40 ± 3,80 dB in the normotensive group. No significant difference was found (p=0.059). The result of audiometry examination was shown in table 2.

Table 1. Result of Hearing Test with OAE and Tympanometry

Examinations	Groups				*P-value*
	Severe preeclampsia		Normotensive		
	n	%	n	%	
Right OAE					
Pass	25	100.0	25	100.0	0.999*
Refer	-	-	-	-	
Left OAE					
Pass	25	100.0	25	100.0	0.999*
Refer	-	-	-	-	
Right tympanometry					
Type A	25	100.0	25	100.0	0.999*
Other types	-	-	-	-	
Left tympanometry					
Type A	25	100.0	25	100.0	0.999*
Other types	-	-	-	-	
Total	25	100.0	25	100.0	

P-value = Chi Square test, p > 0.05

Table 2. Comparison of Hearing Threshold in Severe Preeclampsia Group and Normotensive Group

Audiometry examination	Severe preeclampsia	Normotensive	*P-value*
Right ear	19.69±3.18	20.43±2.19	0.340
Left ear	19.40±3.80	21.10±2.19	0.059

Unpaired T-test

Hearing impairment is defined as AC and BC values more than 25 dB in one or both ears based on audiometry examination. In the severe preeclampsia group, one subject (4.0%) had mild sensorineural hearing impairments (27.75 dB) of the left ear. No hearing impairment was found in normotensive pregnancies.

Prevalence of hearing impairment in severe preeclampsia group was 4% and none found in the normotensive group. Statistical analysis showed no significant relationship was found between severe preeclampsia and sensorineural hearing impairment (p=0.999) (Table 3).

Table 3. Relationship between Severe Preeclampsia and Sensorineural Hearing Impairment

Pregnancies	Hearing impairment				*P-value*
	Yes		No		
	n	%	n	%	
Severe preeclampsia	1	4.0	24	96.0	0.99
Normotensive	0	0.0	25	100.0	9

Fisher test

DISCUSSION

A Continuous condition of oxidative stress in severe preeclampsia causes endothelial dysfunction that potentially disrupt blood flow and blood vessels not only in the placenta but in all maternal blood vessels, including cochlear blood vessels. In the cochlea, hypoxia may cause transient or permanent dysfunction of both outer and inner hair cells, and may even lead to damage of the hair cells, which will lead to sensorineural hearing impairment. These conditions commonly decrease or disappear entirely after termination of pregnancy. This may explain the lack of sensorineural hearing impairment found in this study.[4-8]

From the audiometry test, the mean value of AC and BC of 19,69 ± 3,18 dB was found in severe preeclampsia group and 20,43 ± 2,19 dB in the normotensive group. Both were within the normal threshold of less than 25 dB. No significant relationship was found between severe preeclampsia and sensorineural hearing impairment in this study.

This finding was in contrast with a study by Bakhshaee that found a significant relationship between severe preeclampsia and sensorineural hearing impairment based on OAE examination. The test in Bakhshaee study was performed in clinics before the patients were referred to central referral hospital and were done two weeks after delivery. On the other hand, this study was held in a central referral hospital, and tests were performed two days after delivery, in which case, patients were assumed to have received appropriate management of severe preeclampsia. It is also assumed that patients referred from smaller health care had received treatment for preeclampsia before being referred to the central referral hospital. This resulted in a protective effect against complications of preeclampsia.The lack of a significant relationship between severe preeclampsia and sensorineural hearing impairment in this study might also be due to the small sample size, 25 subjects in each group.[6,8,9,10]

CONCLUSION

Based on this study, it can be concluded that no early hearing damage, especially in the cochlea, was found in OAE examination. Prevalence of sensorineural hearing impairment in severe preeclampsia was 4% based on audiometry examination. Sensorineural hearing impairment was not found in normotensive pregnancies. There was no significant relationship between severe preeclampsia and sensorineural hearing impairment based on audiometry examination.

SUGGESTION

Further study with a bigger sample size is needed. Hearing tests should be performed in clinics and before delivery.

REFERENCES

1. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, et al. World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol 2006; 194(3): 639-49
2. Kementerian Kesehatan Republik Indonesia. Laporan Kesehatan Ibu Tahun 2014. Jakarta: Direktorat Bina Kesehatan Anak Kementerian Kesehatan Republik Indonesia 2014.
3. Bakhshaee M, Hassanzadeh M, Nourizadeh N, Karimi E, Moghiman T, Shakeri M. Hearing impairment in pregnancy toxemia. J Otohns. 2008; 139; 298-300.
4. Baylan MY, Kuyumcuoglu U, Kale A, Celik Y, Topcu I. Is preeclampsia a new risk factor for cochlear damage and hearing loss? .Otol Neurotol. 2010; 31:1180-3.
5. Terzi H, Kale A, Hasdemir PS, Selcuk A, Yavuz A, Genc S. Hearing loss: An unknown complication of pre-eclampsia?. J Obstet Gynecol. 2015; 41: 188-92.
6. Altuntas E, Yenicesu A, Mutlu A, Muderris S, Cetin M, Cetin A. An evaluation of the effects of hypertension during pregnancy on postpartum hearing as measured by transient-evoked otoacoustic emissions. ACTA otorhinolaryngol It 2012;32:31-6.
7. Prawirohardjo S, Pre-eklampsia dan Eklampsia, dalam Ilmu Kebidanan, Editor: Wiknjosastro H, Saifuddin A, Rachimhadhi T, ed ke-3, Jakarta: Yayasan Bina Pustaka Sarwono Prawirohardjo, 2005: 281-301
8. Ozdemir I, Yilmaz S, Albayrak M, Guclu E, Hearing Evaluation in Preeclamptic Patients, Gynecol Obstet Invest 2011;72:1–4
9. Young, Brett C., Richard J. Levine, and S. Ananth Karumanchi. "Pathogenesis of preeclampsia." Ann Rev Path Mech Dis 5 2010: 173-92.
10. Baylan MY, Kuyumcuoglu U, Kale A, Celik Y, Topcu I. Is preeclampsia a new risk factor for cochlear damage and hearing loss? Otol Neurotol. 2010; 31:1180-3

Research Article

Factors Affecting the Drop Out Rate of Family Planning Intrauterine Device

Hubungan Faktor-Faktor yang Mempengaruhi Drop Out Peserta Akseptor Keluarga Berencana IUD dengan Tingkat Kepatuhan

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Abstract

Objective : To assess the association between risk factors related to IUD acceptors' compliance at RSMH Palembang.

Methods : This cross-sectional study was conducted in the Department of Obstetrics and Gynecology Dr. Mohammad Hoesin Hospital/Faculty of Medicine Universitas Sriwijaya Palembang since May - December 2017. Subjects were women who use IUD contraceptives in the Department of Obstetrics and Gynecology Dr.MohammadHoesin Hospital Palembang and meet our inclusion and exclusion criteria. Medical counselling, knowledge, and side effects were assessed using a questionnaire. Data were analyzed by Chi-square test using SPSS software version 17.

Results : There was a significant relationship between side effects and compliance of IUD use. There was no significant correlation between knowledge and medical counselling with compliance of IUD.

Conclusions : Side effects associated with compliance of IUD.

Keywords : compliance, contraception, IUD.

Abstrak

Tujuan : *Mengetahui hubungan faktor-faktor risiko yang bermakna dalam mempengaruhi kepatuhan peserta akseptor IUD di RSMH Palembang.*

Metode : *Penelitian potong lintang ini dilakukan di Departemen Obstetri dan Ginekologi Rumah Sakit Dr. Mohammad Hoesin/Fakultas Kedokteran Universitas Sriwijaya Palembang sejak Mei – Desember 2017. Sampel penelitian ini adalah perempuan yang menggunakan kontrasepsi IUD di Departemen Obstetri dan Ginekologi Rumah Sakit Dr. Mohammad Hoesin/Fakultas Kedokteran Universitas Sriwijaya Palembang dan memenuhi kriteria inklusi dan eksklusi. Konseling medik, pengetahuan, dan efek samping dinilai dengan menggunakan kuesioner. Data dianalisis dengan uji Chi square menggunakan SPSS versi 17.*

Hasil : *Ada hubungan bermakna antara efek samping IUD dengan kepatuhan pemakaian IUD. Tidak ditemukan hubungan bermakna antara tingkat pengetahuan dan konseling medic dengan kepatuhan akseptor IUD.*

Kesimpulan : *Efek samping IUD mempengaruhi kepatuhan pemakaian IUD.*

Kata kunci : *IUD, kontrasepsi, kepatuhan.*

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INTRODUCTION

Indicators of successful health development in Indonesia are expected to be achieved if the percentage of acceptors of the long-term method of contraception (Metode Kontrasepsi Jangka Panjang/MKJP) increases.[1] MKJP is a long-term (more than two years), effective and efficient contraception to postpone pregnancy for more than three years or to stop pregnancy in couples who do not want another child. Contraceptive methods included in this group are sterilization, implant, and Intra Uterine Device (IUD).[2]

IUD contraception is very effective and long-term contraceptive method, but it is less desirable because insertion procedure is quite complicated and must be done by trained medical personnel. IUD is considered as a taboo because it has to be inserted into acceptor's genital; this is why women are often afraid during IUD insertion. IUD also has some complications or side effects

that cause uncomfortable feelings such as heavy menstruation, dysmenorrhea, and intermenstrual bleeding, which can cause anaemia. Perforation of the uterine wall may occur if insertion is incorrect. These side effects and complications decrease the number of IUD users. In some cases, side effects of IUD cannot be overcome with only administration of drugs, and in the end, acceptors will discontinue IUD.[3,4]

Drop out rate of IUD is 9.9%.[5] Reasons for non-compliance with IUD use are contraceptive failure, dissatisfaction, side effects, and lack of availability of birth control devices. The high rate of drop-out, failure and replacement of family planning tools indicate that improvement is needed in the provision of counselling services for potential users, follow-up services and wider service provision.[1,2,6]

Research conducted in Jakarta showed that from all acceptors who received counselling before and after IUD insertion, 90% still used IUDs in the first year, and 79% in the second year. Meanwhile, in other group receiving counselling only when there were any complaints, and the compliance rates were lower (52% and 29%). Low level of IUD usage is due to a lack of acceptors' knowledge about the advantages of this method. This is due to incomplete information provided by health care workers.[7] 10% of all dropout cases are due to fear of side effects and other health problems. A study in El Salvador in 2002 found that high levels of IUD non-compliance were caused by rumours, lack of attention during counselling and health worker's skills.[8]

This study aims to determine the level of compliance and factors influencing drop out of IUD acceptor at Mohammad Hoesin Hospital (RSMH) Palembang.

METHODS

This cross-sectional study was conducted in the Department of Obstetrics and Gynecology of Dr. Mohammad Hoesin Hospital Faculty of Medicine Universitas Sriwijaya, Palembang from May until December 2017. Sample of this study is women who use IUD contraceptives in the Department of Obstetrics and Gynecology Dr. Mohammad HoesinHospital and meet our inclusion and exclusion criteria. Single parents were excluded from the study sample. Medical counselling, knowledge, and side effects were assessed using a questionnaire. Based on validity and reliability test, this questionnaire was valid ($p < 0.05$; $r > 0.576$ (r table with n = 10; 95% CI)) and realible (Cronbach's alpha = 0.733). Data were analyzed by Chi square test using SPSS software version 17.

RESULTS

During the study period, there were 60 mothers with a history of IUD use, 21 mothers could not be reached by phone, four mothers refused to participate in this study, and six mothers agreed to participate but did not attend the meeting. Finally, we obtained 39 women as research samples.

From 39 women, 28 women (71.8%) were still using IUD, while 11 women (28.2%) decided to remove IUD (drop out). Characteristics of the study sample are shown in table 1. Obstetric characteristics of the study sample are shown in table 2.

Table 1. General Characteristics of Study Subjects

Characteristic	IUD		*P-value*
	Yes	No	
Age (year), mean ± SD	27.23 ± 5.89	25.36 ± 3.982	0.318[a]
Age, n (%)			
< 20	2 (7.1)	1 (9.1)	0,654[b]
20-35	24 (85.8)	10 (90.9)	
>35	2 (7.1)	0 (0)	
Residency			
Downtown	28 (100)	11 (0)	1[c]
Suburban	0 (0)	0 (0)	

Education, n(%)			
Uneducated	0 (0)	2 (18.2)	0.150[b]
Elementary school	6 (21.4)	3 (27.2)	
Junior high school	2 (7.1)	1 (9.1)	
Senior high school	17 (60.7)	5 (45.5)	
University	3 (10.8)	0 (0)	
Employment, n (%)			
No	6 (21.4)	1 (9.1)	0.649[c]
Yes	22 (78.6)	10 (90.9)	
Total	28	11	

[a]*Independent T Test*, p= 0.05, [b]*Pearson Chi-Square*, ¬p = 0.05, [c]Fisher Exact, ¬p = 0.05

Table 2. Obstetric Characteristics of Study Subjects

Characteristic	IUD		*P-value*
	Yes	No	
Number of pregnancies, n (%)			
1	11 (39.3)	5 (45.5)	0.526[a]
2-4	14 (50.0)	6 (54.5)	
> 4	3 (10.7)	0 (0)	
Number of delivery, n (%)			
1	13 (46.4)	6 (54.5)	0.639[a]
2-4	13 (46.4)	5 (45.5)	
> 4	2 (7.2)	0 (0)	
History of pregnancy loss, n, (%)			
No	23 (82,1)	11 (100)	0.296[b]
Yes	5 (17.9)	0 (0)	
Number of children, n (%)			
None	0 (0)	1 (9.1)	0.396[a]
1	13 (46.4)	5 (45.5)	
2-4	14 (50.0)	5 (45.5)	
> 4	1 (3.6)	0 (0)	
Contraceptive history, n(%)			
Non IUD	2 (7.2)	6 (54.5)	0.003[b]
IUD	26 (92.8)	5 (45.5)	
Total	28	11	

[a]Pearson Chi-Square, ¬p = 0.05, [b]Fisher Exact, ¬p = 0.05

In this study, all respondents both in drop out and non drop out group considered that they recievesatisfactory counselling. Therefore, we can not analyze this variable.

Table 2. Association between Medical Counselling, Knowledge and Side Effects with Drop Out of IUDAcceptor

Characteristic	IUD		Total	PR* (CI 95%)	*P-value*
	No.	Yes			
Counselling					
Low	0	0	0	2.5454	1
High	11	28	39		
Knowledge				2.8	0.282
Low	1	0	1	(2.232-6.469)	
High	10	28	38		
Side effects				4,800	0.041
High	3	18	21	(1.034-22.239)	
Low	8	10	18		

*Fisher Exact, p value = 0.05

Only one respondent (2.6%) in drop out group had low knowledge level, while in non drop group out 100% had high knowledge level. In Fisher Exact test, we found a relationship between knowledge level and drop out rate. Women with low knowledge level were 2.8 times more likely to drop out than women with high knowledge level, but this relationship was not statistically significant (PR = 2,800; p = 0.282).

A total of 18 respondents experienced high side effects (46.1%), and 44.4% of them chose to remove IUDs. A total of 21 respondents experienced mild side effects (53.8,1%), and 14,2% of them chose to remove IUD. In the Fisher Exact test, we found a significant association between side effects and drop out rates. Acceptor experienced high side effects 4.8 times more likely to drop out than acceptors with low side effects (PR = 4,800; p = 0.041).

Twenty-eight respondents continued to use IUDs. The main reasons for IUD compliance were medical conditions (32.14%), and the second most reason is because of its practicality.Eleven respondents decided to remove IUDs. The main reasonfor IUD removal was side effects (36.4%) and prohibited by husbands or families (36.4%).

From the Logistic Regression test, we concluded that side effects were associated with IUD dropout, women who had side effects were 4.2 times more likely to drop out compared to women without side-effects (Table 4). However, this relationship was not statistically significant (p> 0.05).

Table 4. Factors Associated with IUD Drop out

Variable	Unadjusted*		Adjusted**	
	PR	*P-value*	PR	*P-value*
Medical counselling	2.545	1	-	-
Knowledge	3.800	0.282	<0.001	>0.999
Side effects	4.800	0.041	4.200	0.071

**Chi Square test,* **Logistic regression

DISCUSSION

We found that 28.2% of women decided to remove IUDs. This finding is higher than the national dropout rate of 9.9%.[5] Higher IUD dropout rates in this study may be due to the effect of sample selection.Our study sample is women in productive age who tend to be reluctant to choose long-term contraceptives;Influence of husbands and families is also important because Indonesia is a strong paternalistic country and husbands' participation during counselling sessions is still very rare besides that, our study sampleis small and may not be representative of the actual population.

Based on respondents' characteristics, there were no differences in age, education and occupation between droup out and non-drop out group (p value >0.005). We also found no significant association between obstetric history and IUD compliance.

Many studies have shown that medical counselling is important in improving acceptors' compliance in the selection and use of IUD. A study in Jakarta showed that 90% of family planning participants who received counselling before and after IUD insertion still used IUD in the first year, and 79% in second years. Study in Sri Lanka also showed that family planning participants who received counselling had lower IUD drop out rate than those who did not receive counseling.7This study showed that if patients were satisfied with services provided by health workers, their compliance would increase. In this study, all respondents both in drop out and non drop out group considered that they satisfied with counselling provided by the health workers. So wecan not conclude whether medical counselling affects acceptors' compliance of IUD usage. This finding is similar to study which foundgood quality of medical counselling and attitudes toward contraceptive support at RSMH, in both physicians and midwives.[9]

Almost all study respondents in both groups had a high level of knowledge. This may be related to good medical counseling, which provides adequate information to IUD acceptors. We did not find any significant relationship between levels of knowledge with compliance of IUD use (p> 0.05). Research by Utamiet a in Postpartum ward of RSUP DR. M. Djamil showed a significant correlation between knowledge with the unmet need of post partum contraception and post-placental IUD. In general, unmet need for post-placental IUD do not know that IUD can be installed within 10 minutes after delivery.[10] It is not known whether knowledge of our respondents is correlated with the level of education and medical counselling, so further research is needed to analyze the association between knowledge of respondents before and after medical counselling about IUD.

Side effects of contraception can directly influence the continuity of contraceptive use. Juliaan suggests that the main reason for couples of childbearing age do not use contraception is due to contraceptive side effects. This study found a significant association between IUD side-effects and IUD compliance.If IUD side effects are high, IUD acceptors tend to discontinue IUD usage. This finding, when added to the result of a good level of knowledge, indicates that IUD acceptor at RSMH is critical in IUD use. Nevertheless, multivariate analysis did not find a significant association between medical counselling, knowledge, and side effects with IUD compliance.

In addition to side effects of IUD, support of husbands and families is critical to IUD compliance. Support and attention of the husband to his wife will have a positive effect on the marriage relationship. Although the woman has requested permission from her husband to use certain contraceptives, if a complaint arises such asvaginal discharge or discomfort during intercourse, man tends to encourage women to stop using contraceptives.[11,12]

On the other hand, the main reason for IUD compliance is medical conditions, particularly preeclampsia. This indicates that there is a "compulsion" factor to use IUD besides good medical counselling and woman's level of knowledge. Further research is needed to examine this factor, especially the support of husbands and families.

This study has not been done in RSMH Palembang, and similar studies are still rarely done in other regions in Indonesia. Results of this study are expected to be used as a reference for further research in other regions. This study has several limitations, including small sample size due to study time limitation, and did not include other variables that may contribute to compliance of IUD use such as husband and family support.

CONCLUSION

There was a significant relationship between side effects and compliance of IUD use, and there was no significant correlation between knowledge and medical counselling with compliance of IUD.

SUGESSTION

The best suggestion is giving from this research that husband and family must be involved in the counselling of IUD. Further study with bigger sample size, and examine variables such as consellor, husband and family's role, and influence of economic status, believe and religion is needed in the future.

REFERENCES

1. Manurung S. Model pengambilan keputusan meningkatkan akseptor keluarga berencana metode kontrasepsi jangka panjang. J Kes Mas Nas 2013; 7;11: 483-8
2. Prihyugiarto, Mujianto. Analisa Lanjut SDKI 2007, Kelangsungan pemakaian Kontrasepsi. Jakarta: Puslitbang KB dan Kesehatan Reproduksi, BKKBN. 2009;1-29.
3. Marlinda.Hubungan persepsi perempuan usia subur tentang IUD dengan motivasi penggunaan ulang IUD di Wilayah Kerja Puskesmas Lintau Buo III Kabupaten Tanah Datar. Universitas Andalas. 2011.
4. Utami S. Hubungan efek samping dengan kejadian drop out pada Akseptor AKDR di Poli KB I RSUD Dr.Soetomo Surabaya. J Penelitian Kes Suara Forikes.2011; II(3): 144-51.
5. Witjaksono. Rencana aksi keluarga berencana dan kesehatan reproduksi tahun 2012-2014. Jakarta: Badan Kependudukan Keluarga Berencana Nasional (BKKBN). 2012.
6. Bappenas. Evaluasi pelayanan keluarga berencana bagi masyarakat miskin (keluarga prasejahtera/KPS dan keluarga sejahtera-I/KS I. Diakses tanggal 10 Nopember 2015. http://www.bappenas.go.id/pelayanan-keluarga-berencana-bagi-masyarakat-miskin.html.
7. Fisher AA, DE Silva V. Satisfied IUD acceptors as family planning motivators in Sri Lanka. Stud in Fam Plann. 1986;17(5):235-42.
8. Katz KR, Jhonson LM, Janowitz B. Carranza, J.M. Reason for the Low of IUD Use in El Salvador, Int Family Planning Perspective. 2002;28(1):26
9. Basir, Firmansyah. Penelitian Evaluatif Program Pelayanan Keluarga Berencana RumahSakit di Rumah Sakit Mohammad Hoesin Palembang. Tesis. Fakultas Kesehatan Masyarakat Program Pascasarjana Kajian Administrasi RumahSakit, Universitas Indonesia, Depok. 2017.
10. Utami I, Anwar M, Kurniawati HF. PengaruhIntra Uterine Device (IUD) Postplasenta terhadap Involusi Uterus. J Keb Keperawatan. 2016;12(2):120-34.
11. Hartanto, Hanafi, Keluarga Berencana dan Kontrasepsi. Penerbit Pustaka Sinar Harapan, Jakarta.2010
12. Stanford A, Mechanism of action of intrauterine devices: update and estimation of post sterilization effects. AJOG. 2002;187(6)1699-708.

Research Article

Knowledge, Attitude, and Behaviour of Midwives towards Emergency Contraception

Tingkat Pengetahuan, Sikap dan Perilaku Bidan terhadap Kontrasepsi Darurat

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Abstract

Objective : To investigate the level of knowledge, attitude, and behaviour of midwives to emergency contraception in Indonesia.

Methods : This study used a cross-sectional design. Subjects were midwives who worked in the District Cipondoh Tangerang, Banten, Indonesia until the number of subjects is met at least 100 people. The data were collected by using written questionnaires made by researchers based on previous studies with similar themes. The data obtained will be reported descriptively for categorical variables. The analysis results are presented in the form of sum (n) and percentage (%) (proportion).

Results : Of the 100 respondents who answered the questionnaire, 83% of the midwives had a good knowledge of the condition. Good midwife attitude toward EC in public health care and private practices were 84.62% and 85.06%, respectively. Accordingly, the good behaviour shown by midwives in public health care and private practice is 100% and 94.25%. However, from the question qualitatively the level of knowledge, attitude and behaviour of midwives is still classified as less.

Conclusions : The level of knowledge, attitude and behaviour of midwives towards emergency contraception is said to be lacking. Training on EC on midwives is still needed for practical use in the community.

Keywords : emergency contraception, midwife, unwanted pregnancy, uterine contraception

Abstrak

Tujuan : *Mengetahui tingkat pengetahuan, sikap, dan perilaku bidan terhadap kontrasepsi darurat di Indonesia.*

Metode : *Penelitian ini menggunakan desain potong lintang dengan pengambilan sampel berturut-turut. Peneliti mengambil semua subjek yaitu bidan yang bekerja di wilayah Kecamatan Cipondoh Kabupaten Tangerang sampai jumlah subjek minimal terpenuhi sebanyak 100 orang. Pengambilan data dilakukan dengan menggunakan kuesioner tertulis yang dibuat oleh peneliti berdasarkan penelitian-penelitian terdahulu dengan tema serupa. Data yang diperoleh akan dilaporkan secara deskriptif untuk variable kategorik. Hasil analisis disajikan dalam bentuk jumlah (n) dan persentase (%) (proporsi).*

Hasil : *Dari 100 responden, 83% bidan mempunyai pengetahuan yang baik terhadap kontraspsi darurat. Sikap bidan yang baik terhadap kontrasepsi darurat di puskesmas dan di praktik swasta adalah 84,62% dan 85,06%, berturut-turut. Sejalan dengan itu, perilaku yang baik ditunjukkan oleh bidan di puskesmas dan di praktik swasta adalah sebesar 100% dan 94,25%. Namun dari pertanyaan secara kualitatif tingkat pengetahuan , sikap dan prilaku bidan masih tergolong kurang.*

Kesimpulan : *Tingkat pengetahuan, sikap dan perilaku bidan terhadap kontrasepsi darurat dikatakan masih kurang. Masih dibutuhkan pelatihan tentang kontrasepsi darurat pada bidan agar penggunaannya efektif di masyarakat.*

Kata kunci : *alat kontrasepsi dalam rahim, bidan, kehamilan tidak diinginkan, kontrasepsi darurat.*

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INTRODUCTION

Pregnancy is the birth right of all women, so every woman has the right to determine her reproductive health problems, including determining when she is pregnant and what contraceptive protection she will use. If the pregnancy is not planned, or contraception fails to protect it, then this pregnancy can undoubtedly cause problems.[1]Data in the United States that the incidence of unwanted pregnancy as much as 46% of the total number of births in 2006 (CDC).[2] In one study it was suggested that unwanted pregnancies would harm pregnancies, the child to be born, and directly to social health.[3]

Unwanted pregnancies bring new problems,

termination of pregnancy, whether done by medical personnel and non-medical personnel. The act of illegal abortion can pose a danger of complications and is one of the most important causes of maternal morbidity and mortality.[4]In addition, unwanted pregnancy is associated with an increased risk of low birth weight, and preterm delivery was significantly higher among children and delays and poor lactation in mothers.[5-7]

One of the most effective methods to solve with the adverse effects of pregnancy events is Emergency Contraception (EC).[8] These contraceptives can be used after a partner has sexual intercourse without contraceptive protection, and offers a second chance to prevent an unwanted pregnancy.[9]To support the use of EC, medical workers are needed to be placed on the front lines, especially in the field of women's reproductive health; among others, one of them is a midwife. Through the existing study data show not much research conducted to know the knowledge of midwife about EC, therefore midwife as medical personnel in the front line in Indonesia needs to know the knowledge of EC so that the use of EC on well prepared and can reduce the number of adverse pregnancy events in particular in Indonesia country.

METHODS

This study is a cross-sectional study conducted from January to August 2017 in Tangerang District. The minimum subject used in this research is at least ten samples according to the big sample count. The research was conducted at the Public Health Center and Clinic of the private midwife in Tangerang Regency. The study period started from January 2017 until August 2017. The affordable population was then divided into two groups, midwives working in Tangerang sub-district health centres and midwives working in self-employment practices. Data were collected by using written questionnaires made by researchers based on previous studies with similar themes. In the questionnaire, there are 31 questions about knowledge (20 core questions), ten questions about attitude, and five questions about behaviour. Data analysis was performed with SPSS 20.3. Moreover, we also performed a qualitative analysis of the questions given to the respondents.

RESULTS

From the distribution of data on the questionnaire based on 100 respondents, the population result was 13 (13%) of the respondents working in Public Health Care, and 87 (87%) were employed in private practice. Characteristics of the subjects are presented in Table 1.

Table 1. Characteristics of the Subjects

Characteristics of social and demographic midwives	n	%
Workplace		
Public health care	13	13
Private clinic	87	87
Age (yo)		
20-30	40	40
31-40	32	32
41-50	13	13
>50	15	15
Last education		
Diploma 3	71	71
Bachelor	27	27
Master	2	2
Length of work (yo)		
< 5	23	23
5 – 10	41	41
10 – 20	15	15
> 20	21	21
Attend contraceptive training		
Ever	39	39
Never	61	61
Attending Seminar		
Never participate	0	0
Once a year	32	32
Four times a year	67	67
More than four times a year	1	1

The average age of respondents is predominantly in the 20-30 year age group of 40 respondents (40%). Most of the respondents had the last education background of midwifery diploma of 71 respondents (71%), followed by bachelors of 27 respondents (27%).

Distribution of long working group of respondents in the group of 5-10 years is 23 people (23%). Most of the respondents had never attended Emergency Contraception training for 61 people (61%). The average respondents had attended seminars on health, with the most frequent frequency of 4 times a year, with 67 respondents (67%).

Midwives Knowledge of Emergency Contraception

Most of the respondents, as many as 83 people (83%), can answer questionnaires questions and categorize good knowledge of emergency contraception. The rest have sufficient knowledge of emergency contraception as much as 17 respondents (17%), and no less knowledgeable.

From the distribution of midwives' work to the knowledge of EC presented in Table 2, midwives working in public health care all had good knowledge of 13 (13%) EC. Almost all midwives working in private practice can answer all questions well, but around 17 (19.54%) of respondents from the private midwife group can only answer questions with sufficient knowledge.

Table 2. Midwives Knowledge of Emergency Contraceptionwith Place of Work

		Workplace	
		Public health care (n=13) %	**Private clininc (n=87) %**
Knowledge	Enough	0 (0)	17 (19.54)
	Good	13 (100)	70 (80.46)
Total		13 (100)	87 (100)

Overall, midwives' knowledge is good enough, but when viewed from the question distribution in Table 3, it is known that many midwives lack the knowledge of emergency contraception.

Table 3. Distribution of Knowledge Questions on Emergency Contraception

	Public health midwives (n = 13) %	**Private clinic midwives (n = 87) %**
Never heard of emergency contraception.	13 (100)	87 (100)
Knowing the exact definition of emergency contraception	4 (30.8)	42 (48.3)
Contraceptive methods are emergency contraception		
Implant	13 (100)	
Condom		78 (89.7)
Tubectomy		1 (1.1)
IUD		8 (9.2)
Maximum time limit for starting emergency contraceptive pills		
One day after the first copulation	8 (61.5)	55 (63.2)
More than two days after copulation	5 (38.5)	27 (31)
Once diagnosed with pregnancy		5 (5.7)
One week before having sex		
Emergency contraception pills on the market		
Postinor		
Microgynon	13 (100)	81 (93.1)
Primolut		6 (6.9)
Neyna		
What to do if the patient vomits within 2 hours of emergency contraceptive pills		
Continue to the next tablet	1 (7.7)	
Repeat taking medication from the first tablet		14 (16.1)
Move to regular contraception (contraception previously used by the patient)	8 (61.5)	7 (8)
Give anti-vomiting medication and proceed to the next tablet	4 (30.8)	45 (51.7)
		21 (24.2)

Regarding midwives' attitude toward emergency contraception of the entire midwife working in Public health care is only 84.62% who have a good attitude towards emergency contraception in daily use, the rest about 15.38% have a bad attitude. Midwives who work in private practice, from 87 respondents, about 14.94% have less attitude, and 85.06% others have a good attitude.

About midwives' behavior on emergency contraception of all midwives working at Public health care (n =) 13 has good behavior against emergency contraception in daily use, whereas according to midwife respondents working in

private practice (n = 87) about 94, 25% had good behaviours against emergency contraception in daily use, but still there was about 5.7% who behaved less against emergency contraception in the private midwife group.

DISCUSSION

In this study, there are population between midwives who work in Public health care as many as 13 people and who work in private practice as much 87 people. According to the data of the Ministry of Health in 2016, there are quite a lot of midwives working in Tangerang Banten area, about 3914 midwives are employed in Banten.[10] Of the 100 respondents, approximately 83 (83%) midwives have good knowledge, 17 (17%) had sufficient level of knowledge on emergency contraception, and none had less knowledgeable levels of emergency contraception.

Concerning the workplace population on emergency contraceptive knowledge of all midwives working in public health care, 13 midwives (100%) have a good level of knowledge about emergency contraception. However, from the midwives who work in private practice as many as 87 respondents, only about 70 respondents (80.46%) who only have a good level of education, the rest have adequate education. It can be seen that the workplace has no significant difference in figures in outcomes about knowledge of contraceptive cycles. This is because, in addition to the workplace, many factors that affect the level of education, such as information that can be through print media, visual or otherwise.

Overall assessment of midwives knowledge level on emergency contraception has been good, but if we look again at each detail question, there are some interesting things in this research. In this study, all the midwives or respondents who participated in this questionnaire had already heard emergency contraception as much as 100%. But many still do not know the exact definition of emergency contraception. This is possible because it has never received a detailed study of emergency contraception at the time of midwife education. Thus, the next question remains that some small groups of respondents have not been able to specify the exact number of emergency contraception types.

Some of the questions in the knowledge of the condition has not been optimal and shows that midwife knowledge is still lacking in emergency contraception. Another thing that may need to be considered is to remind the midwife that they have competence and authority in the use of contraception, even though the authority on EC has not been written directly.

Of the ten attitude questions given in the questionnaire, statements about abortive emergency contraception are still many midwives who regard EC as an abortive substance. This is due to the lack of knowledge that will make the midwife condone a wrong understanding of EC.

Of the five questions concerning behaviour against emergency contraception shows, there are still some midwives answering questionnaires that exhibit less behaviour. The possibility is that there are still respondents who do not understand correctly about the use of emergency contraception so that the behaviour in giving emergency contraception is not optimal, especially about the provision of condensed to be stored and the prescribing of EC at the indicated 16-17-year-old teenagers.

In the midwife population working in private practice, there are still about 5.7% (n = 5) of respondents having fewer categories of emergency contraception. According to data obtained by a lack of deep understanding of EC, there are still midwives who behave poorly, such as allowing patients to store an EC for later use.

REFERENCES

1. Erbil N, Bostan, Ö. Knowledge and behaviors of nurses and midwives with emergency contraception. Int J Hum Scien, 2010; 7(2) :875-83
2. Sedgh G, Singh S,Hussain R. Intended and unintended pregnancies world wide in 2012 and recent trends. Studies in family planning. 2014;45(3):301-14.
3. Moosazadeh M, Nekoei-Moghadam M, Emrani Z, Amiresmaili M. Prevalence of unwanted pregnancy in Iran: a systematic review and meta-analysis. Int J Health Plan Management. 2014; 29(3): e277-90
4. Tamire W, Enqueselassie F. Knowledge, attitude, and practice on emergency contraceptives among female university students in Addis Ababa, Ethiopia. Department of community health, Faculty of Medicine, Addis Ababa University, Ethiopia. 2007;21:111:6.
5. Gipson JD, Koenig MA, Hindin MJ. The effects of unintended pregnancy on infant, child, and parental health: our view of the literature .Studies in family planning. 2008;39(1):18-38.

6. Shah PS, Balkhair T,Ohlsson A, Beyene J, Scott F, Frick C. Intention to become pregnant and low birth weight and preterm birth: asystematic review. Maternal Child Health J. 2011;15(2):205-16.
7. Abbasi S, Chuang CH, Dagher R, Zhu J, Kjerulff K. Unintended pregnancy and postpartum depression among first-time mothers .J Womens Health (Larchmt). 2013;22(5):412-6.
8. Dominguez L, Downing D, Schwarz E, Trussell J, Wesley E. ARHP's Annual Reproductive Health Clinical Conference: Update on Emergency Contraception. Contracept. 2011; 3 :3-6
9. Nworah JAO, Sunday UM, O. Ugboaja Joseph OOMaC, Josephat A. Knowledge, attitude and practice of emergency contraception among students in tertiary schools in Anambra State Southeast Nigeria. Int J Med Medical Scien 2010; 2(1) :1-4
10. Data and Information Center of the Ministry of Health of the Republic of Indonesia. Indones Health Profile 2015; 3: 57-5.

Research Article

Perineal Body Length and Pelvic Organ Prolapse in Menopausal Women

Panjang Perineal Body dan Prolaps Organ Panggul pada Perempuan Menopause

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Abstract

Objective : To determine the correlation between the perineal body length and the Pelvic Organ Prolapse (POP) in menopausal women.

Methods : The Total Vaginal Length (TVL), Genital Hiatus (GH), and Perineal Body (PB) length as the POP-Q component were measured at 60 menopausal women enrolled in a cross-sectional study.

Results : Menopausal women with POP have the shorter perineal body (63.3%; <3 cm) compared with menopausal women without POP (36.7%; ≥3 cm). The mean length of the perineal body in menopausal women who suffer POP 2.81 ± 0.26 cm while in women without POP is 3.23±0.17 cm. POP risk was 25 times in menopausal women with a perineal body length <3 cm compared with longer perineal body (p = 0.01; OR = 25.4; 95% CI 3.1-209.1).

Conclusions : Perineal body length is a risk factor for pelvic organ prolapse in menopausal women.

Keywords : perineal body, prolapse, pelvic organ prolapsed.

Abstrak

Tujuan : *Menentukan korelasi panjang perineal body dengan kejadian Prolaps Organ Panggul (POP) pada perempuan menopause.*

Metode : *Pengukuran komponen POP-Q meliputi total Vaginal Length (TVL), Genital Hiatus (GH), dan panjang perineal Body (PB) dilakukan pada 60 perempuan menopause yang dilibatkan dalam penelitian potong lintang.*

Hasil : *Perempuan menopause dengan POP memiliki perineal body yang lebih pendek (63,3%; <3 cm) dibandingkan dengan perempuan menopause tanpa POP (36,7%; ≥3 cm). Panjang rata-rata perineal body pada perempuan menopasue yang menderita POP 2,81 ± 0,26 cm sedangkan pada perempuan tanpa POP adalah 3,23 ± 0,17 cm. Risiko POP 25 kali pada perempuan menopause dengan panjang perineal body <3 cm dibandingkan dengan tubuh perineum yang lebih panjang (p = 0,01; OR = 25,4; 95% CI 3,1-209,1).*

Kesimpulan : *Panjang perineal body merupakan faktor risiko prolaps organ panggul pada perempuan menopause.*

Kata kunci : *perineal body, prolapsed, prolaps organ panggul.*

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INTRODUCTION

The weakness of the pelvic floor support structure causes urogenital prolapse. Approximately 50% of parous women will develop prolapse and 10-20% of them with serious symptoms. Prolapse is associated with decreased quality of life and as a cause of pelvic organ dysfunction. Incidence of prolapse increases with age[1]. Approximately 50% of women over 50 years have urogenital prolapse complaints.[2] The etiology of prolapse of pelvic organs is multifactorial, based on epidemiological studies there was evidence that pelvic organ prolapse is associated with parity, particularly multiplying and complicated vaginal delivery.[3]

Pelvic Organ Prolapse Quantification (POP-Q) has been recognized as a worldwide measurement standard.[4] POP-Q component measurements are easy, sensitive and specific to anatomical changes.[5] Perineal body (PB) is measured from the posterior boundary of the genital hiatus (HG) to the midpoint of the anal canal.[3] This study aims to determine the correlation between the perineal body length and the Pelvic Organ Prolapse (POP) in menopausal women.

METHODS

The Health Research Ethics Committee of Medicine Faculty Universitas Hasanuddin,

Makassar approved the study. A cross-sectional study conducted at Wahidin Sudirohusodo Hospital and affiliated hospitals at the Department of Obstetrics and Gynecology at Universitas Hasanuddin from December 2017 to February 2018. The Total Vaginal Length (TVL), Genital Hiatus (GH), and Perineal Body (PB) length as the POP-Q component were measured at menopausal women. Data were analyzed with Chi-square test, and p-value <.05 was considered statistically significant.

RESULTS

Table 1 shows most menopausal women with pelvic organ prolapse aged ≥60 years (88.3%) with 80% had BMI less than 30 kg/m2 and only ten women using hormonal contraception. The study also showed that women with pelvic organ prolapse, all of which had a parity of> 3 compared with 15 women without prolapse. Other characteristics are shorter than 60% in women aged >60 years compared with 60% in women aged <60 years. Women aged> 60 years have a shorter perineal body (p=0.001). Women with PB length <3 cm has had more children (>3) compared with longer PB length. POP risk was 25 times in menopausal women with a perineal body length <3 cm compared with longer perineal body (p = 0.01; OR = 25.4; 95% CI 3.1-209.1).

Table 1. Patients Characteristics

Characteristics	Prolapse		Normal		P-value	OR	95% CI	PB <3 cm		PB ≥3 cm		P-value	OR	OR
	n	%	n	%				n	%	n	%			
Age (years)														
< 60	5	16.7	20	66.7	0.01	10	2.934	1	5.3	24	58.5	0.01	25.4	3.1209.1
≥ 60	25	83.3	10	33.3				18	94.7	17	41.5			
Parity							-							
< 3	0	0	15	50.0	0.01	-		0	0	15	36.6	0.001	–	–
≥ 3	30	100	15	50.0				19	100	26	53.4			
Body mass index (kg/m2)														
< 30	25	83.3	28	93.3	0.42	2.8	0.515.7	15	78.9	38	92.7	0.193	3.4	0.7-16.9
≥ 30	5	16.7	2	6.7				4	21.1	3	7.3			
Using contraception														
No	20	66.7	23	76.7	0.57	0.61	0.2- 1.9	16	84.2	27	65.9	0.246	2.7	0.7-11.1
Yes	10	33.3	7	23.3				3	15.8	14	34.1			

Table 2. Perineal Body (PB) Length in Prolapse and Normal Menopausal Women

PB length (cm)	Prolapse		Normal		*P-value*
	n	%	n	%	
< 3	19	63.3	0	0.0	<0.01
≥ 3	11	36.7	30	100.0	
PB length (mean±SD cm)	2.81±0.26		3.23±0.17		<0.01

Our study found that postmenopausal women with more pelvic organ prolapse had perineal body length <3 cm (63.3%) compared with menopausal women who did not have pelvic organ prolapse had r perineal body >3 cm. The mean length of the perineal body in menopausal women who suffer POP 2.81 ± 0.26 cm while in women without POP is 3.23±0.17 cm (table2).

DISCUSSION

Menopause generally occurs at the age of 45-55 years while the mean age for Indonesian women having menopause at age 50 years. Pelvic organ prolapse found that pelvic organ prolapse increased 16-20% every ten years of age increase. Increased age is also associated with the loss of elastin that leads to the weakness of tissue due to the effects of gravity straightening back the collagen fibres. Although collagen fibres are strengthened up to 400% with the increase of age, the total strength of urogenital tissue decreases by approximately 60%.[6] A study show that most of the women seeking for pelvic floor disorders were 60 years and older.[7]

Parity is also a factor that affects the prolapse of pelvic organs in our study. A study found more

than 90% of pelvic organ prolapse patients are multiparous.[8] Previous study show compared with nulliparous women; multiparous women had the higher risk for prolapse (4-fold vs 8.4-fold risk of prolapse.[9] In addition, the higher risk for prolapse (11-fold) for multiparous compared with nulliparous women.[10] Asian women with high parity have an increased risk of prolapse of the anterior vaginal compartment as European women.[11]

Our study also showed body mass index <30 kg/m2 not as a risk factor of POP in menopausal women. Other studies have shown that overweight and obesity are significantly associated with prolapse in all compartments[12] while suggests that increased BMI is a risk factor for urinary incontinence and alvi but not a risk factor for pelvic organ prolapse.[13]

Another finding of our study is PB length <3cm mostly observed in menopausal women aged >60 years, whereas PB length> 3 cm observed in women aged <60 years. A study shows perineal body <3 cm found in older women compared with younger women with perineal body ≥3 cm.[14] In younger women, collagen 'S' forms easily stretched. In older women, there is increased intercellular and intramolecular collagen crosslinking, causing the 'S' form to become more rigid so that the perineal body tissue may shrink.[6] A previous study found no difference in weight and height between women with a perineal body length <3 cm and ≥3 cm.[15] Similar results were also found that the length of the female perineum was not associated with other anthropometric measurements although height was known to be associated with female pelvic size.[16] However, another study found menopausal women who had pelvic organ prolapse had longer PB length (>3 cm) in white and black women aged 35-64 years with length of PB was 3.94 cm

CONCLUSION

Perineal body length is a risk factor for pelvic organ prolapse in menopausal women.

REFERENCES

1. Swift, SE. Epidemiology of pelvic organ prolapse; in: Ostergard's Urogynecology and Pelvic Floor Dysfunction. 5th edition. Lippincott Williams and Wilkins: Philadelphia. 2003:35-41.
2. Balmfort, J Robinson, D. Pelvic Ogan Prolapse; In Evidence-Based Physical Therapy for Pelvic Floor. Elsevier: Philadelphia. 2007:235-6.
3. Mouritsen L. Classification and evaluation of prolapse. Best Pract Res Clin Obstet Gynecol. 2005;19(6):895-911.
4. Bump, RC, Cundiff, GW. Pelvic Organ Prolapse in Clinical Urogynaecology. 2nd edition. Churchill Livingstone: Philadelphia. 2000:357-70.
5. Pearce M, Swift S, Goodnight W. Pelvic Organ Prolapse: Is there a difference in POPQ exam results based on time of day, morning or afternoon? Am J Obstet Gynecol. 2008;199(2):200.e1-5.
6. Petros, PEP. The female pelvic floor: function, dysfunction and management according to the integral theory. 2nd edition. Springer: Berlin. 2004: 14-5.
7. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol 2001;184:1496-501.
8. Dunivan GC, Lyons KE, Jeppson PC, Ninivaggio CS, Komesu YM, et al. Pelvic Organ Prolapse Stage and the Relationship to Genital Hiatus and Perineal Body Measurements. Female Pelvic Med Recons Sur. 2016;22(6):497-500.
9. Patel DA, Xu X, Thomason AD, Ransom SB, Ivy JS, DeLancey JO. Childbirth and pelvic floor dysfunction: An epidemiologic approach to the assessment of prevention opportunities at delivery. Am J Obstet Gynecol. 2006;195(1):23-8.
10. Siddighi, S. Surgical management of anterior vaginal wall prolapse. In: Siddighi S, Hardesty JS, eds. Urogynecology & Female Pelvic Reconstructive Surgery: Just the Facts. New York, NY: McGraw-Hill; 2006:121-8.
11. Duong TH, Korn A. Predictors of advanced pelvic organ prolapse in Asian women. J Reprod Med. 2009;54(8):488-92.
12. Hendrix SL, Clark A, Nygaard I. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol. 2002;186:1160.
13. Chen CC, Gatmaitan P, Koepp S, Barber MD, Chand B, et al. Obesity is associated with increased prevalence and severity of pelvic floor disorders in women considering bariatric surgery. Sur Obes Relat Dis. 2009;5(4):411-5.
14. Geller EJ, Robinson BL, Matthews CA, Celauro KP, Dunivan GC, et al. Perineal body length as a risk factor for ultrasound-diagnosed anal sphincter tear at first delivery. Int Urogynecol J. 2014;25(5):631-6.
15. Eid SM. Is Perineal Body Length Measurement Reinforcing the Decision About Performance. Or Avoidance of Episiotomy? AAMJ, 2011;9(3) Suppl.-2: 209-28.
16. Deering SH, Carlson N, Stitely M, Allaire AD, Satin AJ. Perineal body length and lacerations at delivery. J Reprod Med. 2004;49(4):306-10.

Research Article

Neurofibrillary Pathology in the Infundibular Nucleus in Relation to Age and Abnormal Hormone Levels

Patologi Neurofibrilar pada Nukleus Infundibularis Terkait Usia dan Kadar Hormon Abnormal

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Abstract

Objective : To determine whether the decline of testosterone during ageing would make this nucleus more vulnerable for NF changes (i.e.hyperphosphorylated-tau) in men, or that the decline of estrogens in the postmenopausal period would protect the infundibular nucleus in women.

Methods : TWe investigated the infundibular nucleus in postmortem subjects. Brain materials obtained from 29 subjects in the Netherlands Brain Bank were further classified as control subjects and subjects with abnormal hormone conditions. Procedures consisted of tissue collection, immunochemical staining, and analysis of the staining intensity. Results then were collected and concluded using observational methods.

Results : Elderly male subjects with low testosterone conditions showed more severe NF changes in the infundibular nucleus than postmenopausal women. The occurrence of NF changes in elderly subjects was generally accompanied by the presence of basket-like nerve terminals staining for ERβ.

Conclusions : The sex difference in NF changes in the infundibular nucleus in the elderly is due to hyperphosphorylated-tau induction in low testosterone and ageing condition in men, while in postmenopausal women the declining estrogen levels seem to protect against NF changes in this brain area.

Keywords : ageing, estrogen, hyperphosphorylated-tau, infundibular nucleus, testosterone

Abstrak

Tujuan : *Untuk menentukan apakah penurunan level testosteron selama proses penuaan menyebabkan nukleus infundibularis menjadi lebih rentan terhadap perubahan neurofibrilar (NF) (misalnya hyperphosphorylated-tau) pada laki-laki atau apakah penurunan level estrogen selama masa pasca-menopause memiliki efek protektif terhadap nukleus infundibular pada perempuan.*

Metode : *Peneliti memeriksa nukleus infundibular pada subjekpost-mortem. Materi berupa jaringan otak dari 29 subjek dari Netherlands Brain Bank lebih lanjut diklasifikasikan sebagai subjek kontrol dan subjek dengan kondisi hormon abnormal. Prosedur terdiri dari pengumpulan jaringan, pewarnaan dengan teknik imunohistokimia, dan analisis dari intensitas pewarnaan. Hasil yang didapat kemudian dikumpulkan dan disimpulkan sesuai dengan metode observasional.*

Hasil : *Subjek laki-laki lanjut usia dengan testosteron rendah menunjukkan perubahan NF yang lebih buruk pada nukleus infundibular dibandingkan dengan perempuan postmenopause. Kejadian perubahan NF pada subjek lanjut usia secara umum diikuti oleh munculnya pewarnaan pada ujung saraf berbentuk basket-like yang positif untuk Erβ.*

Kesimpulan : *Perbedaan jenis kelamin terkait perubahan NF pada nukleus infundibular pada subjek lanjut usia terjadi akibat induksi hiperfosforilasi tau pada kondisi testosteron yang rendah yang dikombinasi oleh proses penuaan pada pria. Sedangkan pada perempuan pascamenopause, penurunan level estrogen menunjukkan efek protektif terhadap perubahan NF pada area otak ini.*

Kata kunci : *estrogen, hiperfosforilasi protein tau, nukleus infundibularis, penuaan, testosteron.*

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INTRODUCTION

The infundibular nucleus (arcuate nucleus) of the hypothalamus is considered to be the central site of regulation of the Hypothalamus Pituitary Gonadal (HPG) axis and metabolism.[1] Hyper-phosphorylated tau-containing neurofibrillary (NF) pathology, which is often observed in the infundibular nucleus of the hypothalamus of Alzheimer's disease patients, is also present in the hypothalamus of cognitively intact elderly subjects. This NF pathology shows a striking sex difference: it is almost exclusively present in the infundibular nucleus of cognitively intact older men and occurs only rarely in cognitively intact elderly women.[2]

In postmenopausal women, a subset of neurons in the infundibular nucleus becomes strongly activated, as indicated by an increased soma size, larger nuclei containing nuclear spheroids, larger and multiple nucleoli, and increased Nissl substance. In postmenopausal women and in young subjects with a surgical menopause an increased gene expression was found in infundibular nucleus neurons for estrogen receptor (ER), neurokinin-B (NKB), substance-P (SP), and gonadotropin-releasing hormone (Gn-RH). A series of observations strongly suggest that the loss of inhibitory feedback of estrogens on the hypothalamus causes this increased neuronal hyperactivity in postmenopausal women. In addition, some hypertrophied neurons, but to a much lesser degree than in women, were observed in older men.[3] In our previous study in the infundibular nucleus, a shift was observed from a more nuclear localization of ERα in young females to more cytoplasmic localization of ERα in non-demented postmenopausal women.[4] This shift in ERα localization was accompanied by a relative absence in the expression of NF pathology, i.e. hyperphosphorylated-tau stained by AT8, and was considered to be another sign of neuronal activation. Therefore, we considered the sex difference in NF pathology as one of the many examples of neurons that were highly active or strongly activated in the elderly and seemed to be protected against the occurrence of NF pathology, a phenomenon we described as "use it or lose it".[5]

In non-demented older men, only a small increase in cytoplasmic ERα was found, accompanied by NF pathology in the infundibular nucleus. In addition, the occurrence of NF pathology in non-demented older men was accompanied by the presence of more ERβ basket-like nerve terminals in the infundibular nucleus.[4]

In order to determine whether the gradual diminishment of testosterone in men during aging would induce NF pathology or the strong decline of estrogens in postmenopausal women would protect the infundibular nucleus neurons against NF pathology, we investigated this nucleus in postmortem material of patients with abnormal hormone conditions.

METHODS

Tissue collection

Postmortem material was obtained from the Netherlands Brain Bank (coordinator Dr. Rivka Ravid). Permission was obtained for a brain autopsy and the use of brain material and clinical information for research purposes. Hypothalami of 13 subjects with abnormal circulating gonadal steroids levels, i.e. castrated, estrogen-treated male-to-female (MF) transsexuals; an ovariectomized testosterone-treated female to male (FM) transsexual; castrated prostate cancer patients; an ovariectomized woman; a subject with complete androgen insensitivity syndrome (CAIS); a subject with an estrogen-producing adrenal tumour, a subject with an androgen-producing adrenal tumour (Table. 2), and 16 age and sex-matched control subjects (Table. 1) were studied immunocytochemically and estimated semi-quantitatively. None of the subjects suffered from a primary neurological or psychiatric disease. All the brains were investigated systematically by a neuropathologist.[6] The distribution of the Alzheimer neurofibrillary changes over the brain was estimated according to the stages of Braak and Braak. Six stages of disease propagation can be distinguished with respect to the location of the intraneuronal cytoskeletal changes stained by AT8, i.e. neuropil threads and neurofibrillary tangles, and the severity of changes in the hippocampal formation, in the transentorhinal and entorhinal regions and the adjoining temporal isocortex.[7] The Braak stages I-II, clinically silent cases, are characterized by the formation of neurofibrillary changes limited to

the transentorhinal region. The Braak stages III-IV, incipient AD, are characterized by the severe changes found only in a few allocortical regions and adjoining areas. Stage III reveals the striking destruction of layer Preα within both the entorhinal and transentorhinal regions and is accompanied by mild changes in the hippocampus and the virtual absence of neocortical lesions. At stage IV, additional changes are found in the deep layer of Priα. The Braak stages V-VI, fully developed in Alzheimer's disease, are characterized by the destruction of neocortical association areas.[8]

The hypothalami were formalin-fixed, paraffin-embedded, and cut serially in 6 µm coronal sections. For anatomical orientation, every 100th section was mounted on chrome-alum sulphate-coated glass slides, deparaffinized, hydrated, and stained with thionine (0.1% w/v thionine in acetate buffer, pH 4). The location of the infundibular nucleus was determined based on the human brain atlas[9], and if necessary, with the help of neuropeptide Y (NPY) immunocytochemical staining.[1] The rostral border of the infundibular nucleus was identified at the level where the nucleus showed its characteristic arcuate shape; the cell-sparse zone separating the infundibular nucleus from the ventromedial nucleus (VMN) indicated the dorsolateral border; the ependymal layer of the third ventricle served as the medial border, and the mamillary bodies were taken as the caudal border. Three series of sections per subject were taken from rostral to caudal at approximately 25%, 50% and 75% of the length of the infundibular nucleus, and mounted onto Super-Frost plus (Menzel, Braunschweig, Germany) slides for immunocytochemistry. We took adjacent sections for estrogen receptor (ER)α, ERβ and hyperphosphorylated-tau protein (AT8) immunocytochemical staining. In addition, we also determined the expression of AT8 staining in other areas in the hypothalamus adjacent to the infundibular nucleus, such as the VMN, the nucleus tuberalis lateralis (NTL), the nucleus basalis of Meynert (NBM), and the tuberomammillary nucleus (TMN).

Immunocytochemistry and specificity of the antisera

A polyclonal rabbit anti-ERα antiserum (MC-20) that recognizes the carboxyl-terminus epitope of the ERα (Santa Cruz Biotechnology, Inc., catalogue no. sc-542) and a polyclonal goat anti-ERβ antiserum (N-19), directed against an amino acid sequence mapping at the amino-terminus of human ER β (catalogue no. sc-6820, Santa Cruz Biotechnology, Inc., Santa Cruz, CA) were used in the present study. The staining procedures and specificity tests for ERα and ERβ antisera have been previously described extensively [10-11]. No staining was observed after omitting the MC-20 antiserum or after adsorption of MC-20 to its blocking peptide.[10] In a spot blot test, MC-20 recognized its blocking peptide on nitrocellulose paper by showing the expected concentration gradient (Santa Cruz Biotechnology; blocking peptide, catalogue no. sc-542, lot no.C059). In addition, two different anti-ERα antisera, C-314 (N-terminus directed; Santa Cruz Biotechnology; Catalog no. sc-786; anti-bovine ERα; lot no.J278) and MC-20 (C-terminus directed) displayed similar distribution patterns in the human hypothalamus. Western blot with the ERα antiserum MC-20 on human hypothalamic tissue showed a specific band around the expected 68 kDa, with no such band around the 54 kDa of ERβ.[11] Western blot with the ERβ antiserum N-19 on human hypothalamic tissue recognized a protein band around expected 54 kDa weight and did not recognize the 68 kDa protein band i.e. ERα.[12] In spot blots it was also confirmed that the antiserum N-19 recognizes the homologous blocking peptides, while an adsorption test with the homologous peptide resulted in elimination of the staining.[10] Moreover, staining of adjacent sections with the antiserum against the C-terminus of the ERβ (L-20, Santa Cruz Biotechnology, Inc, catalogue no. sc-6822)[13] revealed the same staining pattern as the antiserum against the N-terminus of ERβ used in the present study[10]. ERβ cytoplasmic staining was observed in granulosa cells, and follicles of the human ovary, a localization which is consistent with a study in the rat.[14] In human testis, Leydig and connective tissue cells showed nuclear ERβ staining, which is also in agreement with a study in the rat.[15] The differences in distribution shown by the ERα antiserum MC-20 and the ERβ antiserum N-19 in the hypothalamus, pituitary, ovary and testis, as described extensively by [10-11]series of observations demonstrated that the ERα and β antisera used in our study were specific.

For immunocytochemical staining of hyper-phosphorylated-tau, a primary monoclonal antiserum AT8 directed against the phosphorylated-tau

epitopes serine 202 and threonine 205 was used.[16] This antiserum was used to recognize hyperphosphorylated-tau as an early marker for the neurofibrillary AD pathology. The staining procedure was performed.[2]

Earlier studies showed that the variability in fixation and postmortem time does not influence the staining of ERα, Eβ or AT8.[4]

Analysis of the staining intensity

Two independent investigators, blind to the subject's condition, judged the staining intensity of the sections. The staining intensity of ERα and β in the cytoplasmic and nuclear compartment was estimated semi-quantitatively by means of light microscopy, based on the number of stained neuron and basket-like nerve terminals in the infundibular nucleus, and graded according to the following scale: (+++) strong, (++) moderate, (+) weak, (+/-) very weak and (-) absent, according to our previous studies.[16] The semi-quantitative estimation for neuropathological changes in AT8-staining was judged according to the number of stained neurons and neuropil threads in the infundibular nucleus and graded as the following scale: (++++) severe, (+++) marked, (++) moderate, (+) mild, (0) no discernible changes as described.[2]

Control subjects

Female controls did not show NF pathology as stained by AT8 in the infundibular nucleus, while mild changes were only observed in the two oldest males (#15, #16). Staining of hyperphosphorylated-tau was absent in other hypothalamic or adjacent brain areas in controls.

Hypertrophied neurons and nuclear spheroid-containing neurons were present in two elderly female controls (#6, #7), while fewer of such changes were observed in another elderly female (#8) and the two oldest male controls (#15, #16; Figure. 2). Using adjacent sections, we observed that the hypertrophied neurons in the two oldest male controls (#15, #16) did not show NF pathology.

Cytoplasmic ERα was observed more often in the infundibular nucleus of female controls than in male controls, while more nuclear ERα was observed in male controls than in female controls. Only weak staining of both nuclear and cytoplasmic ERβ was observed in the infundibular nucleus of male and female controls (Figure. 1). Basket-like ERβ-staining was observed more in males than in females.

RESULTS

Table 1. AT8, ERα and ERβ Staining in the Infundibular Nucleus of Control Subjects

NBB	Age	Sex	Bw(g)	Pmd(h)	Fix(d)	BS	AT8	ERα (INF)		ERβ (INF)			Cause of death
								N	C	N	C	B	
86032	33	F	1035	41.00	20	0	-	2+	-	+	+	+	AdenoCa metastases to the brain
80008	35	F	1200	08.00	26	0	-	3+	-	-	+	+	Acute lymphoblastic leukaemia
96423	49	F	1253	<17.00	806	0	-	±	2+	2+	+	-	Massive thromboembolism
98125	58	F	991	06.15	41	I	-	+	2+	-	±	-	Multiple organ failure
98035	65	F	ID	<20.00	31	0	-	+	+	-	+	-	Mesenteric ischemia
99085	69	F	1102	<02.30	120	0	-	±	2+	-	+	-	Uremia
93139	78	F	1135	06.25	32	0	-	-	2+	±	+	+	Bronchopneumonia
96084	78	F	1330	07.30	26	II	-	2+	+	-	±	-	Pulmonary emphysema
-	+	2+	-	±	-								
98121	47	M	1420	<82.30	31	0	-	±	±	-	+	-	Cardiac arrest
97159	48	M	1500	05.30	42	0	-	2+	±	-	±	2+	Multiple organ failure
93072	50	M	1573	<09.00	52	0	-	+	+	-	+	+	Hypovolemic shock
97139	59	M	1400	<65.45	180	0	-	±	+	-	±	-	Pulmonary embolism
98122	66	M	1461	<41.00	49	0	-	2+	+	-	+	+	Septic shock
96426	69	M	1222	14.00	728	0	-	2+	2+	±	±	-	Septic shock
97116	80	M	1380	06.56	33	0	+	3+	+	+	±	-	Pulmonary emphysema
94076	78	M	1442	08.25	24	II	+	2+	+	-	±	2+	Myocardial infarction
-	+	2+	-	±	-								

Abbreviations: AdenoCa: adenocarcinoma, AT8: specific staining for hyperphosphorylated-tau, B: basket-like, BS: Braak score, Bw: brain weight (in grams), C: cytoplasmic staining, ER: estrogen receptor, F: female, Fix: fixation time (in days), ID: incomplete data, INF: the infundibular nucleus, N: nuclear staining, NBB: Netherlands Brain Bank number, M: male, Pmd: postmortem delay (in hours).

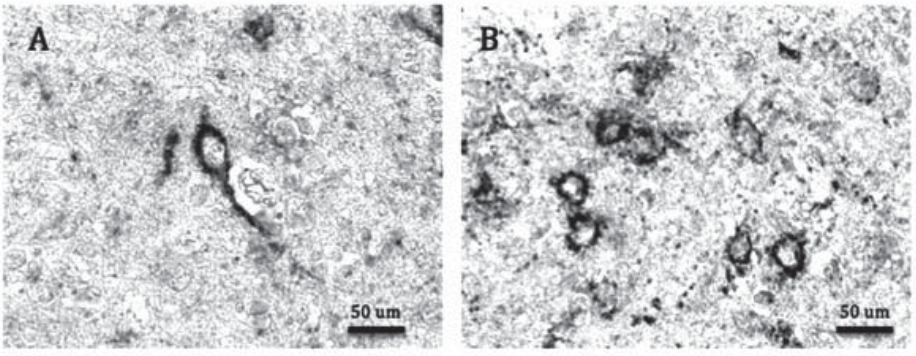

Figure 1. Photomicrograph depicting basket-like nerve terminals containing estrogen receptor (ER)β immunoreactivity (IR) in the infundibular nucleus. Hypogonadal prostate cancer patients (subject #20)(B) showed more of such baskets with a higher intensity of ERβ-IR than elderly male controls (subject #16)(A). Scale bar: 50 µm.

Subjects with abnormal hormone conditions

All subjects that underwent castration because of prostate cancer showed AT8 positive staining in the infundibular nucleus, independent of whether they were treated or not treated with anti-androgen. Five patients in this group (#17, #18, #19, #20, #21) showed more severe NF pathology than observed in elderly male controls (Figure. 2). Two of these patients (#17, #21) also showed hyperphosphorylated-tau in other hypothalamic and adjacent brain areas, i.e. the ventromedial nucleus (VMN), the nucleus tuberalis lateralis (NTL), the nucleus basalis of Meynert (NBM) and the tuberomammillary nucleus (TMN) (Table. 2).

The subject with complete androgen insensitivity syndrome (CAIS) (#22), who had received estrogen substitution, did not show NF pathology in the infundibular nucleus. The 74-year-old male-to-female (MF) castrated, and estrogen-treated transsexual (#25) had moderate AT8-staining in the infundibular nucleus, whereas in two younger MF transsexuals (#23, #24) the presence of hyperphosphorylated-tau was not observed. A female to male (FM) transsexual subject (#27) of 51 years of age who had been treated with testosterone showed no AT8-staining. Negative AT8-staining in the infundibular nucleus was also observed in the 46-year-old ovariectomized female (#26), in a 46-year-old female with an androgen-producing adrenal tumour (#28) and in a 31-year-old male with an estrogen-producing adrenal tumour (#29).

An absent to weak staining of nuclear ERα and a weak to moderate staining of cytoplasmic ERα were observed in prostate cancer patients, MF transsexual subjects, ovariectomized woman and an FM transsexual. A moderate nuclear ERα and a very weak to moderate cytoplasmic ERα-staining were observed in the CAIS subject and in subjects with sex steroid-producing adrenocortical carcinoma.

All subjects with abnormal hormone conditions showed an absent to very weak nuclear ERβ-staining and a very weak to weak cytoplasmic ERβ-staining.

Subjects with low levels of testosterone showed relatively more basket-like ERβ than elderly control subjects (Figure. 1).

The occurrence of hyperphosphorylated-tau in a subset of neurons in the infundibular nucleus of elderly males in low testosterone conditions was generally accompanied by the presence of basket-like ERβ in nerve terminals (#18, #19, #20, and #25).

The hypertrophied neurons were observed more in elderly castrated prostate cancer patients than other subjects with abnormal hormone conditions. These neurons showed histological signs of hyperactivity, i.e. larger cell size, a larger nucleus and nucleolus compared to the surrounding neurons and the presence of nuclear spheroid bodies. They were observed easily, either localized inside or outside basket-like ERβ nerve terminals. Remarkably, these hyperactive neurons never showed NF pathology. Further details regarding subjects' clinical and endocrinology characteristics are presented in Table 3.

Table 2. AT8, ERα and ERβ Staining in the Infundibular Nucleus and other Brain Areas of Subjects with Abnormal Hormone Conditions

NBB	Diagnosis	Age	Sex	Bw(g)	Pmd(h)	Fix(d)	BS	AT8 (INF)	AT8 in NTL, TMN, VMN, NBM	ERα (INF)		ERβ (INF)			Assumption androgen status as compared to controls	Assumption estrogen status as compared to controls
										N	C	N	C	B		
89103	Prostate cancer	67	M	1290	24:00	28	ID	2+	NTL(2+), TMN(2+), VMN(2+), NBM(2+)	-	+	-	±	±	↓	↓
97157	Prostate cancer	69	M	1475	05:55	45	0	4+	-	±	+	±	+	2+	↓	↓
95062	Prostate cancer	80	M	1400	04:30	24	II	4+	-	±	+	-	±	2+	↓	↓
94109	Prostate cancer	82	M	1110	05:35	32	II	4+	-	±	+	-	±	3+	↓	↓
94090	Prostate cancer	86	M	1663	03:00	93	II	3+	TMN(+), VMN(+), NBM(2+)	+	2+	-	±	+	↓	↓
'02089	CAIS	75	M	1484	06:30	34	I	-	-	2+	2+	-	±	-	↓	↑
84020	MF Transsexual	50	M	1380	ID	30	0	-	-	±	-	-	±	±	↓	↑
93070	MF Transsexual	53	M	1500	<100	34	0	-	-	-	±	-	±	±	↓	↑
98141	MF Transsexual	74	M	1118	06:35	33	I	2+	-	±	2+	-	+	2+	↓	↑
80002	Surgical menopause	46	F	1300	02:30	36	0	-	-	-	+	-	±	-	↓	↓
98138	FM Transsexual	51	F	1171	04:15	32	0	-	-	+	+	-	+	±	↑	↓
83004	Androgen-producing adrenal tumour	46	F	1360	<10:50	34	ID	-	-	2+	±	-	±	+	↑ (measured)	(*)
91005	Estrogen-producing adrenal tumour	31	M	1377	<34:00	35	ID	-	-	2+	+	-	±	2+	Slightly ↑ (measured)	↑ (measured)

Abbreviations: AT8: staining for hyperphosphorylated-tau, B: basket-like, BS: Braak score, Bw: brain weight (in grams), CAIS: complete androgen insensitivity syndrome, C: cytoplasmic staining, ER: estrogen receptor, F: female, FM: female to male transsexual, Fix: fixation time (in days), ID: incomplete data, INF: the infundibular nucleus, N: nuclear staining, NBB: Netherlands Brain Bank number, M: male, MF: male to female transsexual, NBM: the nucleus basalis of Meynert, NTL: the nucleus tuberalis lateralis, ORX: orchidectomy, OVX: ovariectomy, Pmd: postmortem delay (in hours), TMN: the tuberomammillary nucleus, VMN: the ventromedial nucleus, (*): cannot be assumed.

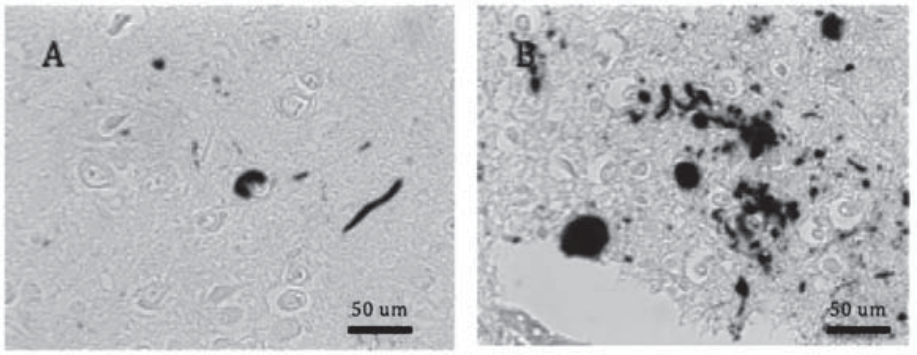

Table 3. Clinical and Endocrine History of Patients with Abnormal Hormone Conditions

Case	No.	Age (yr)	Age of hormonal treatment (yr)	Age of Orchid Ovari-ectomy (yr)	Clinical data and endocrine history	Cause of death
Prostate cancer patients	#17	67	-	67	Orchidectomy 3 months before death, the patient did not receive anti-androgen treatment	Carcinoma of the pancreas with metastases; cachexia
	#18	69	67	67	Orchidectomy 3 years before death, anti-androgen, anandron 150mg 1 dd during three years before death	Prostate cancer with advances metastases
	#19	80	-	75	Orchidectomy 5 years before death, the patient did not receive anti-androgen treatment	Renal insufficiency
	#20	82	-	82	Orchidectomy 20 years before death, the patient did not receive anti-androgen treatment	Prostate cancer, respiratory failure, renal insufficiency
	#21	86	85	85	Memory problem started six years before death. Diagnosis at hospitalization: subcortical dementia. Neuropathological diagnosis: slight alzheimerization, Braak for tangle = II. Orchidectomy 1 year before death. The patient received CPA, anti-androgen, (50mg 4 dd) during the first 14 months, (50 mg 2 dd) during the last six months	Prostate cancer, lung cancer and septic shock
CAIS	#22	75	70	55	Orchidectomy 20 years before death, the patient received 17β-estradiol (2mg 1 dd) during the last five years before death and stopped two months before death.	Advance state of squamose cell vagina carcinoma

MF-trans sexuals	#23	50	42	44	Age 42: stilbestrol (5 mg 1 dd); after 2 months to (5 mg 2 dd); age 44: CPA (50 mg 2 dd); treatment lasted 4 years; stopped 2 years before death; ethinylestradiol (50 µg 2 dd); treatment lasted 8 years until death	Suicide
	#24	53	40	50	Age 40: stilbestrol treatment (stopped after 1 yr); at age 43–47: Premarin (0.625 mg dd); at age 47–50: Premarin (3.75 mg dd); at age 50–53: Premarin (2.5 mg 3 dd); CPA (50 mg 1 dd); topical estrogen cream (estrogen treatment stopped 3 months before death)	Acute fatty liver due to alcohol abuse
	#25	74	64	64	Age 64: received CPA treatment (50 mg 2 dd) and ethinyl estradiol (50 µg 2 dd) treatment; at age 67: received Estraderm (100 µg 1 dd); at age 74 received spironolactone (50 mg 1 dd) and Estraderm (100 µg 1 dd)	Coma post-appendicitis, pneumonia, lung embolism, and cerebral occipital infarction
Surgical Menopause	#26	46	-	45	Bilateral ovariectomy 22 months before death, the patient did not receive hormone treatment	Septicemia and ovarian cancer
FM-transsexual	#27	51	27	32	Bilateral ovariectomy at age 32. At age 27 testosterone, Sustanon (250 mg), twice a month injections; at age 30 testosterone undecanoate (40 mg 3 dd); at age 34 testosterone undecanoate (40 mg 2 dd); at age 36 testosterone undecanoate (40 mg 4 dd); at age 44 testosterone, Sustanon (250 mg) twice a month injections; at age 47–48 testosterone, Sustanon (250 mg) every 3 weeks. No testosterone replacement therapy during the last three years before death	Cachexia
Androgen-producing adrenal tumour	#28	46	-	-	Female patient with a virilizing adrenocortical carcinoma for 1 yr that produced high levels of cortisol, androstenedione, and testosterone levels; latest androstenedione serum level before death was 48.0 ng/ml (normal range for women 0.4–3.5 ng/ml); the latest serum testosterone level before death, 26.82 nmol/L (normal range for women is 1.04–3.30 nmol/L).	Adrenocortical carcinoma; postoperative haemorrhage
Estrogen-producing adrenal tumour	#29	31	-	-	Male patient with the recurrent of feminizing adrenocortical carcinoma for 3 yr that produced high levels of DHEA-S, DHEA, 17-hydroxyprogesterone, and estradiol levels; the latest estradiol serum levels 1 yr before death was around 689-732 pmol/L (normal range for men is 50-200 pmol/L); the latest testosterone levels 1 year before death was around 28.9-41.3 nmol/L (normal range for men is 10-30 nmol/L)	Advance metastasis of recurrent adrenocortical carcinoma

Abbreviations: CAIS: complete androgen insensitivity syndrome, CPA: cyproterone acetate, DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone-sulphate, No: numbers corresponding with table 2.

DISCUSSION

The infundibular nucleus, a key structure in the regulation of reproduction and metabolism[1] shows remarkable neurofibrillary (NF) changes in cognitively intact subjects (with Braak stage 0-II). The NF pathology in the infundibular nucleus is characterized by neurofibrillary tangles, a network of neuropil threads and terminal-like portal vessel-associated processes. This NF pathology shows a striking sex difference. From 60 years onwards the prevalence of neurofibrillary changes in the infundibular nucleus of cognitively intact elderly males rises from 20% up to 90% around the age 80-85 years, while in only 6-10% of cognitively intact elderly females such changes were observed.[2, 4] These sexually dimorphic NF alterations should be related to changes in reproduction and metabolism, rather than to cognitive deficits, as observed in AD in other brain areas. Earlier we found, e.g. more NF alterations in the nucleus basalis of Meynert (NBM) in AD women as compared to AD men[17], a difference that may be related to cognition and a sex difference in this disease.

In postmenopausal women, the abrupt decline in the circulating estrogen levels[18] and diminished negative feedback of estrogens on the infundibular nucleus neurons[19] is accompanied by a strong activation of neurons in this brain area as shown by neuronal hypertrophy and increased amounts of estrogen receptors (ER), neurokinin B (NKB) or substance P (SP) gene transcripts in this nucleus.[3] In older men more gradually decreasing plasma testosterone levels are observed[20] accompanied by a lesser degree of neuronal hypertrophy.[8] We hypothesized that the activation of infundibular nucleus neurons that is most pronounced in women would make this sub-population of neurons less vulnerable to the process leading to NF pathology.[4]

The present study indicates that the sex difference in NF changes in the infundibular nucleus in older adults may be due to hyperphosphorylated-tau induction in older men as a result of low testosterone levels. The gradual decline of testosterone in the course of normal aging[20], as also assumed to be present in two elderly male controls (#15, #16), was accompanied by a mild to moderate NF pathology in the infundibular nucleus, confirming earlier studies.[2, 4] In elderly prostate cancer patients, the strong and abrupt decline of serum testosterone following orchidectomy (#18, #19, #20, #21) was accompanied by a much stronger NF pathology in the infundibular nucleus as compared to controls. This NF pathology occurred independently of the fact whether subjects did (#18, #21) or did not (#17, #19, #20) receive anti-androgen treatment following orchidectomy (Tables. 2, 3). Hyperphosphorylated-tau as stained by AT8 was also observed in other brain areas in low testosterone conditions such as the ventromedial nucleus (VMN), the nucleus tuberalis lateralis

(NTL), the nucleus basalis of Meynert (NBM) and the tuberomammillary nucleus (TMN) (#17, #21) and was accompanied in one patient (#20) with subcortical dementia symptoms, suggesting that low testosterone levels may be involved in the development of NF pathology in cognition-related area in the hypothalamus, i.e. NBM. From our ongoing study, AT8 positive staining was also observed in the infundibular nucleus in two Prader-Willi syndromes (PWS) subjects, a 49-year-old male and a 64-year-old female, who generally have low estrogen and testosterone levels, and hypogonadism since early life.[21] In addition, NF pathology was present in the infundibular nucleus of a 74-year-old castrated-MF transsexual subject, who was treated with a combination of estrogens and cyproterone acetate. This also suggests, but of course does not prove, that estrogens do not protect against the formation of NF changes in this brain area.

The observation that two relatively young male orchidectomized patients (#23, #24) did not show any NF pathology in the infundibular nucleus, in contrast to the six elderly castrated men, suggests that the process of ageing is another requirement for the formation of NF pathology. The importance of age in the development of NF pathology in the infundibular nucleus is reinforced by the increase in this neuropathology in the course of normal aging in men[2,4], which is accompanied by a gradual decline of testosterone levels[20] and by the mild NF pathology that was present in the 2 elderly control subjects in the present study (#15, #16). Indirect evidence that lower circulating androgen levels were present in the older men, as compared to the younger ones, comes from the observation that less staining for androgen receptors was observed in the elderly patients in the medial mamillary nucleus. This hypothalamic area is very sensitive to circulating androgen levels as reported earlier.[22] In Kreb's cycle, mitochondria use testosterone for enzymatic reactions in aerobic metabolism and lead to the production of high-energy phosphate compounds.[23] In addition, aging is also related to mitochondrial DNA mutation. Since the brain is highly dependent on aerobic metabolism, it suggests that aging and low testosterone levels may reduce energy and metabolic activities of neurons in the infundibular nucleus, thus increase the risk of neurons to have NF pathology.[24]However, the exact contributions for the factors age and low testosterone levels on the formations of NF pathology have to be studied further.

In a previous study, we found that a subset of proopiomelanocortin (POMC) neurons in the infundibular nucleus co-expresses hyperphosphorylated-tau as stained by AT8, both in cognitively intact elderly males and in AD patients.[4] In the rodent, the cellular POMC mRNA content in the arcuate nucleus was significantly lower in old males than in young males.[25] Moreover, the abruptly decreased testosterone levels following castration of adult male rhesus monkeys results in a strong suppression of the mRNA production of POMC neurons.[26] This indicates that indeed both ageing and low testosterone conditions may contribute to reduced metabolic activity of POMC neurons in the hypothalamus and so increase the risk of these neurons to develop NF pathology in males. α-Melanocyte-Stimulating Hormone (MSH), derived by post-translational processing of the POMC gene product, facilitates penile erection in males.[27] The observation that AT8-positive staining in the infundibular nucleus is only found in a subset of α-MSH producing neurons4 points to the possibility that the occurrence of hyperphosphorylated-tau in the infundibular nucleus may be related to the incidence of erectile dysfunction in elderly males.[28]In our present study, low testosterone conditions also seemed to increase the risk for elderly males to get NF pathology in areas which are related to memory and attention (i.e. the NBM and TMN) (#17, #21).

Circulating total testosterone in men results both from testicular Leydig cell secretion and from peripheral conversion of dehydroepiandrosterone (DHEA) and dehydro¬epi¬androsterone sulphate (DHEA-S), that are produced by the adrenals.[29] Approximately 90% of the serum testosterone in men originates from the testes, whereas only 67% of the serum testosterone in women is secreted by the ovaries.[30] Whether there is a change in free testosterone levels in postmenopausal women is a controversial topic in literature. Some cross-sectional studies indicate that menopause is associated with decreased testosterone, both in total and free testosterone levels.[31] The decline in testosterone levels around menopause would occur over the first three years of the postmenopausal period, while the levels would remain relatively

constant over the following five years.[32] However, another longitudinal study reported that the total testosterone levels might remain stable across the menopausal transition, while the amount of bioavailable testosterone would even increase as Sex Hormone-Binding Globulin (SHBG) levels decrease in postmenopausal women.[33] In addition, a drop in testosterone levels during peri-menopause with increasing testosterone levels in the following two years was observed in another study.[18] Moreover, increased levels of both total and bioavailable testosterone were observed in intact postmenopausal women after adjusting for Body Mass Index (BMI). Most of the increase occurred after 50-59 years, reaching premenopausal levels in the 70-79 decade with relatively stable levels thereafter.[34] Concluding, probably no major decline occurs in free testosterone levels in postmenopausal women. Moreover, the infundibular nucleus in men has more intense staining for the Androgen Receptor (AR) than in women[35], which suggests a more pronounced direct effect of androgens on neuronal functioning in men than in women in this brain area.

In a previous study, the shift from more nuclear localization of ERα in young females to more cytoplasmic ERα in the infundibular nucleus neurons in cognitively intact post¬menopausal women were found to be related to neuronal hyperactivity and lower vulnerability of these neurons to develop NF pathology.[4] In the present study, this observation was confirmed in the controls, while there was no consistent shift of ERα localization found in the patients with abnormal hormone conditions.

In a previous study, we observed the occurrence of basket-like nerve terminals staining for ERβ in the infundibular nucleus of older men and AD patients in relation to NF pathology.[4] In the rodent, the cellular POMC mRNA content in the arcuate nucleus was significantly lower in old males than in young males.[25] Moreover, the abruptly decreased testosterone levels following castration of adult male rhesus monkeys results in a strong suppression of the mRNA production of POMC neurons.[26] This indicates that indeed both ageing and low testosterone conditions may contribute to reduced metabolic activity of POMC neurons in the hypothalamus and so increase the risk of these neurons to develop NF pathology in males. α-Melanocyte-stimulating hormone (MSH), derived by post-translational processing of the POMC gene product, facilitates penile erection in males.[27] The observation that AT8-positive staining in the infundibular nucleus is only found in a subset of α-MSH producing neurons[4] points to the possibility that the occurrence of hyperphosphorylated-tau in the infundibular nucleus may be related to the incidence of erectile dysfunction in elderly males.[28]In our present study, low testosterone conditions also seemed to increase the risk for elderly males to get NF pathology in areas which are related to memory and attention (i.e. the NBM and TMN) (#17, #21).

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In a previous study, we observed the occurrence of basket-like nerve terminals staining for ERβ in the infundibular nucleus of older men and AD patients in relation to NF pathology.[4]

In the present study, the occurrence of hyperphosphorylated-tau in elderly hypogonadal men was, however, generally found to be accompanied by the presence of basket-like nerve terminals staining for ERβ in the infundibular nucleus. Our ongoing study showed that such basket-like ERβ containing terminals might co-express Glutamic-Acid Decarboxylase (GAD) immunoreactivity as a marker for the inhibitory transmitter γ-aminobutyric acid (GABA).[36] The neurons inside the ERβ staining basket tended to be larger and to have a larger nucleus and nucleolus than the surrounding neurons, which suggests that the neuron inside a basket is strongly activated and remains free of NF changes in the middle of NF neuropathology, as we also observed in AD patients.[4] We hypothesized, therefore, that ERβ-mediated inhibition of the GABAergic terminals may induce an increased activity of the neurons inside the basket and thus prevent the formation of hyperphosphorylated-tau in this subpopulation of neurons, which is in line with the phenomenon we described as "use it or lose it".[5]

CONCLUSION

In conclusion, the sex difference in NF changes in elderly controls may be due to hyperphosphorylated-tau induction by low testosterone conditions such as observed here in the combined conditions of castration and ageing in males. The levels of SHBG reinforce the decrease in serum concentration of free testosterone in older men.[37] Since testosterone substitution may prevent the formation of heat shock-induced hyperphosphorylation of tau in rats[38], further investigation of the efficacy of testosterone substitution therapy for delaying or preventing the occurrence of NF pathology in the hypothalamus of elderly males seems worthwhile. The increased activity of some neurons in the infundibular nucleus of hypogonadal elderly males, probably mediated by surrounding basket-like nerve terminals containing ERβ, is accompanied by an absence of neurofibrillary pathology, even in the middle of NF changes in this nucleus. This phenomenon, which is also present in postmenopausal women[5] indicates a new mechanism in the local prevention of NF pathology.

CONFLICT OF INTEREST

Nil.

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REFERENCES

1. Swaab DF. Chapter II Neurobiology and neuropathology of the human hypothalamus. In: Bloom FE, Björklund A, Hökfelt T, editors. Handbook of Chemical Neuroanatomy. 13: Elsevier; 1997: 39-137.
2. Schultz C, Braak H, Braak E. A sex difference in neurodegeneration of the human hypothalamus. Neuroscience letters. 1996;212(2):103-6.

3. Rance NE, McMullen NT, Smialek JE, Price DL, Young WS, 3rd. Postmenopausal hypertrophy of neurons expressing the estrogen receptor gene in the human hypothalamus. J Clin Endocrinol Metabol. 1990;71(1):79-85.
4. Hestiantoro A, Swaab DF. Changes in estrogen receptor-alpha and -beta in the infundibular nucleus of the human hypothalamus are related to the occurrence of Alzheimer's disease neuropathology. J Clin Endocrinol Metabol. 2004;89(4):1912-25.
5. Swaab DF. Brain aging and Alzheimer's disease, "wear and tear" versus "use it or lose it". Neurobiol Aging. 1991;12(4):317-24.
6. van de Nes JA, Kamphorst W, Ravid R, Swaab DF. Comparison of beta-protein/A4 deposits and Alz-50-stained cytoskeletal changes in the hypothalamus and adjoining areas of Alzheimer's disease patients: amorphic plaques and cytoskeletal changes occur independently. Acta Neuropathol. 1998;96(2):129-38.
7. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239-59.
8. Rance NE, Uswandi SV, McMullen NT. Neuronal hypertrophy in the hypothalamus of older men. Neurobiol Aging. 1993;14(4):337-42.
9. Garey LJ. Atlas of the Human Brain. J Anatomy. 1997;191(Pt 3):477-8.
10. Ishunina TA, Kruijver FP, Balesar R, Swaab DF. Differential expression of estrogen receptor alpha and beta immunoreactivity in the human supraoptic nucleus in relation to sex and aging. J Clin Endocrinol Metabol. 2000;85(9):3283-91.
11. Kruijver FP, Balesar R, Espila AM, Unmehopa UA, Swaab DF. Estrogen receptor-alpha distribution in the human hypothalamus in relation to sex and endocrine status. J Compar Neurol. 2002;454(2):115-39.
12. Kruijver FP, Balesar R, Espila AM, Unmehopa UA, Swaab DF. Estrogen-receptor-beta distribution in the human hypothalamus: similarities and differences with ER alpha distribution. J Compar Neurol. 2003;466(2):251-77.
13. Kuiper GG, Shughrue PJ, Merchenthaler I, Gustafsson JA. The estrogen receptor beta subtype: a novel mediator of estrogen action in neuroendocrine systems. Frontiers Neuroendocrinol. 1998;19(4):253-86.
14. Fitzpatrick SL, Funkhouser JM, Sindoni DM, Stevis PE, Deecher DC, Bapat AR, et al. Expression of estrogen receptor-beta protein in rodent ovary. Endocrinol. 1999;140(6):2581-91.
15. Saunders PT, Fisher JS, Sharpe RM, Millar MR. Expression of oestrogen receptor beta (ER beta) occurs in multiple cell types, including some germ cells, in the rat testis. J Endocrinol. 1998;156(3):R13-7.
16. Mercken M, Vandermeeren M, Lubke U, Six J, Boons J, Van de Voorde A, et al. Monoclonal antibodies with selective specificity for Alzheimer Tau are directed against phosphatase-sensitive epitopes. Acta Neuropathol. 1992;84(3):265-72.
17. Salehi A, Gonzalez Martinez V, Swaab DF. A sex difference and no effect of ApoE type on the amount of cytoskeletal alterations in the nucleus basalis of Meynert in Alzheimer's disease. Neurobiol Aging. 1998;19(6):505-10.
18. Overlie I, Moen MH, Morkrid L, Skjaeraasen JS, Holte A. The endocrine transition around menopause--a five years prospective study with profiles of gonadotropines, estrogens, androgens and SHBG among healthy women. Acta obstetricia et Gynecologica Scandinavica. 1999;78(7):642-7.
19. Chakravarti S, Collins WP, Newton JR, Oram DH, Studd JW. Endocrine changes and symptomatology after oophorectomy in premenopausal women. BJOG. 1977;84(10):769-75.
20. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metabol. 2001;86(2):724-31.
21. Crino A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, et al. Hypogonadism and pubertal development in Prader-Willi syndrome. Eur J Pediatr. 2003;162(5):327-33.
22. Kruijver FP, Fernandez-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. J Clin Endocrinol Metabol. 2001;86(2):818-27.
23. Brooks DE. Activity and androgenic control of enzymes associated with the tricarboxylic acid cycle, lipid oxidation and mitochondrial shuttles in the epididymis and epididymal spermatozoa of the rat. Biochemical J. 1978;174(3):741-52.
24. Ojaimi J, Byrne E. Mitochondrial function and Alzheimer's disease. Biological signals and receptors. 2001;10(3-4):254-62.
25. Gruenewald DA, Matsumoto AM. Age-related decrease in proopiomelanocortin gene expression in the arcuate nucleus of the male rat brain. Neurobiol Aging. 1991;12(2):113-21.
26. El Majdoubi M, Ramaswamy S, Sahu A, Plant TM. Effects of orchidectomy on levels of the mRNAs encoding gonadotropin-releasing hormone and other hypothalamic peptides in the adult male rhesus monkey (Macaca mulatta). J Neuroendocrinol. 2000;12(2):167-76.
27. Argiolas A, Melis MR, Murgia S, Schioth HB. ACTH- and alpha-MSH-induced grooming, stretching, yawning and penile erection in male rats: site of action in the brain and role of melanocortin receptors. Brain research bulletin. 2000;51(5):425-31.
28. Carbone DJ, Jr., Seftel AD. Erectile dysfunction. Diagnosis and treatment in older men. Geriatrics. 2002;57(9):18-24.
29. Baulieu EE. Androgens and aging men. Mol Cell Endocrinol. 2002;198(1-2):41-9.
30. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metabol. 1997;82(8):2396-402.
31. Longcope C, Franz C, Morello C, Baker R, Johnston CC, Jr. Steroid and gonadotropin levels in women during the peri-menopausal years. Maturitas. 1986;8(3):189-96.

32. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas. 1995;21(2):103-13.
33. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metabol. 2000;85(8):2832-8.
34. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metabol. 2000;85(2):645-51.
35. Fernandez-Guasti A, Kruijver FP, Fodor M, Swaab DF. Sex differences in the distribution of androgen receptors in the human hypothalamus. J Compar Neurol. 2000;425(3):422-35.
36. Wong CG, Bottiglieri T, Snead OC, 3rd. GABA, gamma-hydroxybutyric acid, and neurological disease. Annals Neurol. 2003;54 Suppl 6:S3-12.
37. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metabol. 2002;87(2):589-98.
38. Papasozomenos SC, Papasozomenos T. Androgens Prevent the Heat Shock-Induced Hyperphosphorylation but not Dephosphorylation of t in Female Rats. Implications for Alzheimer's Disease. Journal of Alzheimer's disease: JAD. 1999;1(3):147-53.

Research Article

Microscopic Examination of Urine Samples as the Early Detection of Asymptomatic Urinary Tract Infection in Pregnant Women: A Cross-Sectional Study

Uji Mikroskopik Spesimen Urin sebagai Deteksi Dini Infeksi Saluran Kemih tidak Bergejala pada Perempuan Hamil: Sebuah Studi Potong Lintang

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Abstract

Objective : To investigate the role of microscopic examination of urine sample in supporting early diagnosis of asymptomatic Urinary Tract Infection (UTI) in pregnant women. To compare correspondence between microscopic examination and urine culture result as a gold standard diagnostic modality to support the diagnosis of UTIs and as an evidence-based to start empirical therapy.

Methods : Microscopic analysis was conducted in 74 centrifuged and non-centrifuged urine samples from 317 pregnant who came to six healthcare centres in Jakarta, which showed a positive result of nitrite examination. The results of the microscopic examination of bacteriuria and leukocyturia were compared with a urine culture.

Results : Sensitivity of centrifuged bacteriuria was the highest among the other microscopic parameters, which was 74% with the p-value of 0.009. Combination of bacteriuria and leukocyturia≥3/HPF dan≥5/HPF have increased the specificity with the value of 91.5% and 93.6% in non-centrifuged urine.

Conclusions : This result showed that the best method of microscopic examination for early diagnosis of asymptomatic urinary tract infection in pregnant women is the detection of bacteriuria in centrifuged urine. Combination of bacteriuria and leukocyturia test, as well as leukocyturia≥3/HPF and≥5/HPF, can be used to rule out the diagnosis of UTI at an early stage.

Keywords : asymptomatic urinary tract infection, bacteriuria, leukocyturia,microscopic examination, urine culture.

Abstrak

Tujuan : *Mengetahui peran pemeriksaan mikroskopis sampel urin dalam mendukung diagnosis dini Infeksi Saluran Kemih asimptomatik (ISK) pada perempuan hamil. Membandingkan kesesuaian antara pemeriksaan mikroskopis dan hasil kultur urin sebagai modalitas diagnostik standar emas untuk mendukung diagnosis ISK dan sebagai dasar bukti untuk memulai terapi empiris.*

Metode : *Penelitian uji mikroskopik dilakukan pada 74 sampel urin disentrifugasi dan tidak sentrifugasi, dari 317 sampel urin perempuan hamil yang berobat ke-enam puskesmas di Jakarta dengan uji nitrit positif. Hasil uji mikroskopik bakteri uria dan leukosit uria dibandingkan dengan hasil kultururin.*

Hasil : *Sensitivitas bakteriuria yang disentrifugasi menunjukan hasil yang paling baik dibandingkan dengan parameter uji mikroskopik lain, yaitu 74% dengan nilai p yang bermakna sebesar 0,009. Kombinasi bakteriuria dan leukosituria ≥3/LPB dan ≥5/LPB dapat meningkatkan spesifisitas uji dengan nilai 91,5% dan 93,6% pada urin yang tidak disentrifugasi.*

Kesimpulan : *Hasil menunjukkan bahwa bakteri uria pada urin yang disentrifugasi, merupakan metode yang paling baik untuk membantu diagnosis dini ISK tidak bergejala pada perempuan hamil. Uji kombinasi bakteri uria dan leukosituria, serta uji leukosituria ≥3/LPB dan ≥5/LPB dapat dimanfaatkan untuk membantu secara dini menyingkirkan orang yang tidak mengalami ISK.*

Kata kunci : *bakteriuria, infeksi saluran kemih tidak bergejala, kultur urin,leukosituria, uji mikroskopik.*

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INTRODUCTION

Urinary Tract Infection (UTI) is the second most prevalent infection in the world, with approximately 8,3 million cases per year.[1]Urinary tract infection is more prevalent in women than in men.[2]

Urine culture is the gold standard test to diagnose UTI. Urine culture is used to isolate, identify, and quantify pathogen, causing UTI, as well as testing for antibiotics sensitivity. Empiric treatment is essential in pregnant women while waiting for culture results. Delayed treatment may harm the mother and fetus, and results in poor pregnancy outcomes, fetal death, and preterm labor.[3]

Therefore, a rapid screening method is needed to diagnose UTI while awaiting culture results and sensitivity test. A microscopic test is one of the rapid screening alternatives for early diagnosis of UTI. To reduce the possibility of false negatives, it is necessary to centrifuge the urine sample to obtain sediments containing the pathogenic microorganisms.[2,3]This study aims to compare results of urine microscopic test, with and without centrifugation, and urine culture.

METHODS

This was a cross-sectional diagnostic study to compare the results of the microscopic test and urine culture to diagnose asymptomatic UTI in pregnant women. A urine sample was collected from pregnant women during prenatal visits in six community healthcare facilities in Jakarta from December 2014 to December 2015. A urine sample was processed in Clinical Microbiology Laboratory, Faculty of Medicine, Universitas Indonesia. We included pregnant women in any trimester who did not consume any antibiotics in the past two weeks and agree to participate in the study. Women with vaginal discharge and fever were excluded. The microscopic test was done in two methods, with centrifugation and without centrifugation of the urine sample, and then Gram staining was conducted. Urine cultures are conducted using blood agar and Mac Conkey agar as a medium in aerobic condition and temperature of 35°C-37°C for 24-48 hour.

Results from microscopic Gram staining were presented as bacteriuria and leukocyturia. Bacteriuria is defined as the finding of bacteria in the urine sample and was presented as positive or negative. Leukocyturia is the finding of leukocytes in the urine sample and is defined as two criteria, ≥5 leukocyte/HPF and ≥3 leukocyte/HPF. Culture results were presented as negative or positive. Results are considered positive if there is a finding of bacterial colony ≥100.000/mL urine. The results from the microscopic test, both with centrifugation and without centrifugation, were compared to urine culture as sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

RESULTS

A total of 74 urine samples were analyzed in microscopic test and urine culture. Urine culture sample resulted in 27 positive culture and 47 negative culture. Results from the microscopic test compared to urine culture are presented in Table 1. Calculated results of sensitivity, specificity, PPV, and NPV of microscopic tests are presented in Table 1.

Table 1. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Microscopic Tests

	Sensitivity %	Specificity %	PPV %	NPV %
Bacteriuria				
Without centrifugation	63	78.7	63	78.7
With centrifugation	74	57.4	50	79.4
Leukocyturia≥3/HPF				
Without centrifugation	3.7	91.5	20	62.3
With centrifugation	7.4	85.1	22.2	61.5
Leukocyturia>5/HPF				
Without centrifugation	3.7	93.6	25	62.9
With centrifugation	3.7	87.2	14.3	61.2

Combined diagnostic results from bacteriuria, leukocyturia≥3/HPF, and leukocyturia≥5/HPF are presented in Table 3. Calculated results of sensitivity, specificity, PPV, and NPV from combined diagnostic results of three microscopic tests are presented in Table 2.

Table 2. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Combined Microscopic Tests

	Sensitivity %	Specificity %	PPV %	NPV %
Positive bacteriuria and leukocyturia≥3/HPF				
Without centrifugation	0	91.5	0	61.4
With centrifugation	7.4	85.1	2.2	61.5
Positive bacteriuria and leukocyturia>5/HPF				
Without centrifugation	0	93.6	0	70
With centrifugation	3.7	87.2	14.3	61.2

Early diagnosis relies on a high sensitivity test. Therefore, Table 3 presents the microscopic tests with the highest sensitivity from each criterion.

Table 3. Microscopic Tests with High Sensitivity

	Sensitivity %	Specificity %	PPV %	NPV %
Positive bacteriuriawith centrifugation	74	57.4	50	79.4
Leukocyturia≥3/HPFwith centrifugation	7.4	85.1	22.2	61.5
Leukocyteuria> 5/HPF without centrifugation	3.7	93.6	25	62.9
Positive bacteriuria and Leukocyturia≥3/HPF with centrifugation	7.4	85.1	22.2	61.5
Positive bacteriuria and Leukocyteuria> 5 /LPB with centrifugation	3.7	87.2	14.3	61.2

DISCUSSION

Bacteriuria Compared with Urine Culture Outcomes

Assessment of bacteriuria in microscopic examination of this study was conducted based on the presence of bacterial findings, Gram staining procedure, and bacterial morphology found. The results are then matched with the urine culture results, which showed the number of correspondence was lower in non-centrifuged urine samples than in centrifuged urine, with a sensitivity of 63% (17/27) versus 74% (20/27). These results showed that the centrifuged urine gives better microscopic test results of bacteriuria finding than the non-centrifuged urine. This value is lower than in a previous study conducted by Wilson et al in Colorado, who obtained sensitivity values for centrifuged urine bacteriuria of 92-100% and with the sensitivity value of 89%.[4,5]

In this study, Gram staining results and the morphology of bacteria species findings derived from urine culture correspond well. In this case, better results were also shown in centrifuged urine bacteriuria compared with non-centrifuged urine, by 95% (19/20) versus 88.2% (15/17) sensitivity. This better results may be caused by cellular elements and other components of biological fluid as well as bacteria being more concentrated as a result of centrifugation.[6]

Viewed from the specificity value, compared with the urine culture results, the bacteriuria of the non-centrifuged urine sample is preferable to the specificity of the centrifuged urine, which is 78.7% versus 57.4%. The value falls within the range of specificity values found in a study conducted by Wilson et al which attained an 8-94% specificity value for bacteriuria in centrifuged urine.[4] The results of this study were slightly lower when compared with a previous study conducted with the specificity value of 85%.[5]

Leukocyturia compared with Urine Culture Outcomes Leukocyturia an interpretative result of microscopic tests which was assessed based on the number of leukocytes contained in the urine. Leukocyturia in this study used two threshold values of leukocyturia≥3/HPF, which is recommended by CDC and leukocyturia>5/ HPF, which were used by some previous studies.[7] The sensitivity of leukocyturia ≥3/HPF found in the Gram staining microscopic test compared with the results of urine culture, which gave significant results with the amount of ≥100,000 CFU/mL colonies, had shown low results in both centrifuged or non-centrifuged urine. The sensitivity of leukocyturia ≥3/HPF compared to urine culture found in centrifuged and non-centrifuged urine samples are of 7.4% and 3.7% value. These results showed that leukocyturia ≥3/ HPF found in centrifuged and non-centrifuged urine microscopic tests are less likely to be used as an alternative for early diagnosis of asymptomatic UTI in pregnant women. However, the results of leukocyturia ≥3/HPF specificity compared with urine culture were better in both treatment types, which were 91.5% in non-centrifuged urine samples and 85.1% in centrifuged urine.

The sensitivity of leukocyturia>5/HPF in both urine samples compared with culture results had shown a similar value of 3.7%. However, compared with urine culture, the specificity value of leukosituria>5/ LPB in non-centrifuged was higher than centrifuged urine, with specificity

values of 93.6% and 87.2%, respectively. Regarding the detection of leukocyturia found in microscopic tests aiming for early diagnosis of asymptomatic UTI, the low sensitivity value of leukosituria>5/ LPB illustrates that this value is also less suitable for both centrifuged and non-centrifuged urine samples.

Combination of Bacteriuria and Leukocyturia in Urine Microscopic Test Compared with Results of Urine Culture

The assessment of the compatibility of combinations of bacteriuria and leukocyturia found in urine microscopic tests compared with urine culture results aimed at increasing the sensitivity of microscopic tests in the early diagnosis of asymptomatic UTI. The combination of bacteriuria and leukocyturia ≥3/HPF in centrifuged urine had a slightly higher sensitivity value than non-centrifuged urine, i.e. 7.4% versus 0%. Similar results were also found in the sensitivity of bacteriuria and leukocyturia>5/ HPF, which showed a slightly higher centrifuged urine sensitivity than non-centrifuged urine of 3.7% compared to 0%. These results indicate that the combination of both bacteriuria and leukocyturia with leukocyturia ≥3/HPF as recommended by CDC or in combination with leukocyturia>5/HPF according to some previous studies, is no better than bacteriuria alone. However, the combination of bacteriuria and leukocyturia gave excellent results in specificity value, both in the non-centrifuged urine and in the centrifuged urine. The specificity value of the combination of bacteriuria and leukocyturia ≥3/ HPF in non-centrifuged and centrifuged urine samples are 91.5% and 85.1%, respectively. The specificity value of bacteriuria and leukocyturia combination>5/HPF is 93.6% in non-centrifuged and 87.2% in centrifuged urine samples. Based on these results, the combination of bacteriuria and leukocyturia is more appropriate for use to exclude instead of to support early diagnosis of asymptomatic UTI in pregnant women.

The Best Urine Microscopic Test Method for Early Diagnosis asymptomatic UTI in Pregnant Women

The highest sensitivity value is a reference for the selection of diagnostic tests for early diagnosis of a disease. In this study, the use of microscopic test of urine samples with various methods was compared with the results of urine culture as a gold standard.[8] Detection of bacteriuria alone in the microscopic urine test obtained in this study, provided the best sensitivity results for use as early diagnosis of asymptomatic UTI in pregnant women, especially when examined from centrifuged urine.[8-10] Statistical analysis using the chi-square test showed a significant p-value of 0.009.

Other parameters are insufficient for use as an early diagnostic tool of asymptomatic UTI in pregnant women, either from a leukocyturia sensitivity alone or a combination of bacteriuria and leukocyturia. The analysis for the significance of these results used the Fischer test because it did not qualify for the chi-square test. The sensitivity value of leukocyturia ≥3/HPF according to the recommendation of CDC was better in centrifuged urine samples (7.4%), but the result of statistical analysis did not show a significance, with a p-value of 0.472. In leukocyturia with parameter>5/HPF according to some previous studies, better sensitivity value in non-centrifuged urine was 3.7%, but the result of analysis also did not show significance with p = 1. Analysis of the combination of bacteriuria with leukocyturia ≥3/HPF showed better sensitivity results in centrifuged urine, with a sensitivity value of 7.4%, and a non-significant p-value of 0.472. Analysis of the combination of bacteriuria with leukocyturia>5/HPF showed better sensitivity results in centrifuged urine, with a sensitivity of 3.7% and a non-significant p-value of 0.411.

Based on the above data, it can be understood that bacteriuria alone is the best urine microscopic test method for early diagnosis of asymptomatic UTI in pregnant women.[11,12] The use of combination parameters of bacteriuria and leukocyturia did not increase sensitivity but rather increased the specificity of the test. The results of good test specificity on the resultant combinations of bacteriuria and leukocyturia in non-centrifuged urine microscopic tests were as good as the specificity of leukocyturia alone, for both cutoffs of ≥3/HPF and >5/HPF.[13]This results showed that microscopic testing of combination of bacteriuria and leukocyturia or leukocyturia alone could be used to help exclude the diagnosis of asymptomatic UTI in pregnant women.

CONCLUSION

The detection of bacteriuria alone in centrifuged urine is the best urine microscopic test method to assist early diagnosis of asymptomatic UTI in pregnant women. However, the combination test of bacteriuria and leukocyturia, as well as leukocyturia alone in both centrifuged and non-centrifuged urine can help rid of early diagnosis of asymptomatic UTI in pregnant women.

The discovery in this study should be used as an alternative to urine culture, to aid early diagnosis of asymptomatic UTI in pregnant women, thus serving as a guide to starting earlier empirical therapy to prevent complications that endanger the mother and the fetus.

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REFERENCES

1. Tessy A, Ardayo, Suwanto. Infeksi Saluran Kemih. Buku Ajar Ilmu Penyakit Dalam Jilid III. 4th Ed. Jakarta: Balai Penerbit FKUI; 2009:369.
2. Sukandar E. Infeksi Saluran Kemih pada Pasien Dewasa. Buku Ajar Ilmu Penyakit Dalam Jilid III. 4th Ed. Jakarta: Balai PenerbitFKUI;2007:553-7.
3. Awonuga DO, Fawole AO, Dada-Adegbola HO, Olola FA, Awonuga OM. Asymptomatic bacteriuria in pregnancy: evaluation of re-agent strips in comparison to microbiological culture. Afr J Med Sci. 2011; 40(4): 377-83.
4. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis. 2004;38(8):1150-8.
5. Lunn A, Holden S, Boswell T. Automated microscopy, dipsticks and the diagnosis of urinary tract infection. Arch Dis Child. 2010;95(3):193-7
6. Ocviyanti D, Fernando D. Tata Laksana dan Pencegahan Infeksi Saluran Kemih pada Kehamilan. Indones Med Assoc 2012; 62(12): 483.
7. Paolo G, Vijaya BR, Odile D, Daniel J. Ureter, Urinary Bladder, and Kidney. 3rd Ed. Philadelphia: Elsevier Saunders; 2010:515-20.
8. Burd EM, Kehl KS. A Critical appraisal of the role of the clinical microbiology laboratory in the diagnosis of urinary tract infections. J Clin Microbiol. 2011; 49(9):815-34.
9. Jeff AS, William CM, John JP. Urinalysis: A comprehensive review. Am Fam Physician. 2005; 71(6):1153-62.
10. Alastair DH. Managing UTI in primary care: Should we be sending midstream urine samples? Br J Gen Pract. 2010; 60(576): 479–80.
11. Thairu Y, Nasir IA, Usman Y. Laboratory perspective of gram staining and its significance in investigations of infectious diseases. Sub-Saharan Afr J Med 2014;1:168-74.
12. Memisogullan R, Yuksel H, Yildirim HA, Yavuz O. Performance Characteristics of dipstick and microscopic urinalysis for diagnosis of urinary tract infection. Eur J Gen Med. 2010;7(2):174-8.
13. Kurup R, Leich M. Comparison of urine analysis using manual and sedimentation methods. J West Ind Med.2012; 61(3):17-9

Research Article

Diagnostic Value of Transvaginal Ultrasonography to Determined Degree of Myometrium Invasion in Endometrial Cancer

Nilai Diagnostik Ultrasonografi Transvaginal dalam Menilai Kedalaman Invasi ke Miometrium pada Kanker Endometrium

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Abstract

Objective : : To show transvaginal ultrasound accuracy in determining the degree of myometrial invasion of endometrial cancer within five years in RSCM. Also, to know histopathology characteristics of endometrial cancer according to cell type, degree of invasion, and degree of differentiation of endometrial cancer, within the last five years in RSCM.

Methods : This study is a cross-sectional study with a sample of 82 subjects in January 2011 – December 2016 at RSCM. The data were collected by total sampling from cancer registry Oncology and Gynaecology Division of Obstetrics and Gynecology FKUI-RSCM.

Results : Transvaginal USG diagnostic test in detection invasion has sensitivity, specificity, PPV, and NPV as 78.79%, 50%, 86.67%, 36.36% respectively. For determine degree of myometrial invasion it has sensitivity, specificity, PPV, and NPV as 81.40%, 76.92%, 79.55%, and 78.90% respectively.

Conclusions : Transvaginal ultrasound has better accuracy in determining the degree of invasion compared to detecting myometrial invasion in endometrial cancer. In determining the degree of invasion, its sensitivity and specificity are 81.4% and 76.92%. For detecting any invasion its sensitivity and specificity was only 79.41% and 57.14%. Our study showed that transvaginal ultrasound was an efficient diagnostic tool fo determine further treatment and prognosis in endometrial cancer.

Keywords : accuracy test, HPV DNA, liquid-based cytology, pre-cervical cancer lesion.

Abstrak

Tujuan : *Mengetahui akurasi USG transvaginal dalam menilai invasi miometrium pada kanker endometrium dalam 5 tahun terakhir di RSCM. Serta karakteristik histopatologi berdasarkan tipe, invasi, dan derajat diferensiasi kanker endometrium dalam 5 tahun terakhir di RSCM.*

Metode : *Penelitian potong lintang dengan jumlah sampel 82 subjek pada Jan 2011 – Des 2016 di RSCM. Data dikumpulkan secara total sampling dari registrasi kanker Divisi Onkologi Ginekologi FKUI RSCM dan dilakukan uji diagnostik.*

Hasil : *Uji diagnostik USG transvaginal menilai ada tidaknya invasi memiliki sensitivitas, spesifisitas, NPP, NPN sebesar 78,79%, 50%, 86,67%, 36,36%. Sedangkan hasil uji diagnostik usg transvaginal dalam menilai derajat invasi memiliki sensitivitas, spesifisitas, NPP, NPN sebesar 81,40%, 76,92%, 79,55%, dan 78,90%.*

Kesimpulan : *USG transvaginal dalam menilai derajat invasi lebih baik dibanding menentukan ada tidaknya invasi. Sensitivitas, spesifisitasnya 81,4% dan 76,92% dibanding 79,41% dan 57,14%. Dalam hal ini USG transvaginal dapat digunakan sebagai alat bantu diagnostik efisien dalam menentukan tata laksana dan prognosis kanker endometrium.*

Kata kunci : *kanker endometrium, kedalaman invasi, uji diagnostik, USG transvaginal.*

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INTRODUCTION

Endometrial cancer is mostly suffered by postmenopausal women and in fourth place after breast, lung, and colon cancer. Endometrial cancer is the third most found cancer in Indonesia after cervical and ovarian cancer.[1,2] Early detection is the determinant factor in endometrial cancer and can be done by taking endometrial samples (biopsy and curettage) and imaging examination.[3]

Endometrial cancer imaging has many modalities such as MRI, CT-Scan and Sonography. This imaging purpose is to evaluate the depth of invasion and to determine the prognosis of the disease. This can predict the lymphovascular metastases to determine the next operative management (surgical staging).[4] MRI is considered the best diagnostic tool yet expensive, which has 88-90% sensitivity, 84-88% specificity and 86-90% accuracy in determining the degree of myometrium invasion.[5-7]Another modality is ultrasonography (USG) which is used in Indonesia because it is more applicable (cheaper and easier to use).[2,8] In another study about USG, transvaginal USG (5-9MHz frequency) in determining endometrial cancer <50% and > 50% has 69% sensitivity and 79%, with 73% accuracy rate. Gordon, using 5 MHz probe USG with 25 samples showed 75% in specificity and sensitivity, 76% accuracy.[4] In developing countries like Indonesia, transvaginal USG is the main modality because it is cheaper and easier to use. Diagnostic value in USG to detect the degree of myometrial invasion is still little known.

To determine the transvaginal USG accuracy on assessing myometrium invasion in endometrial cancer cases at RSCM for the last five years. This research is also to assess the characteristics such as demographic factor, the degree of myometrial invasion, cell type (histopathology) and the degree of differentiation in endometrial cancer cases.

METHOD

This research is using diagnostic study with 2x2 table and cross-sectional study design. As an addition, descriptive research using cross-sectional study will be used to determine the proportion of the type of cell (histopathology), the degree of invasion staging, and the degree of differentiation. The subjects of this study were registered patient with endometrial cancer which diagnosed within 1st January 2011 until 31st December 2016. Oncology division had the data written in the medical record at RSCM. Patients with other gynecology malignancy which did not perform hysterectomy were excluded from this research. The researcher took and specifically picked all the data from the medical record using inclusion and exclusion criteria. All the subjects were re-registered in research report form, including menopause status, parity, marital history, contraception history, and the degree of myometrial invasion based in preoperative transvaginal USG and post-operation histopathology examination. The cell type and the stage of cancer differentiation will also be examined histopathologically after the operation. Patient with incomplete data will be tracked down.

All the histopathology data about myometrial invasion degree based on preoperative and postoperative transvaginal USG were input in the 2x2 table, using the diagnostic study. The data were inserted into Power and Sample Size Analysis (PASS) to determine the power and alpha value based on used samples. As an addition, proportion based on the degree of invasion, histopathology type and the degree of differentiation were calculated.

RESULT

There were 82 responders data obtained from the medical record based on cancer registry cases by RSCM Oncology Gynecology division from 2011-2015, which exceeds from the research proposal's sample with 70 samples. Samples were taken using total sampling method considering inclusion and criteria exclusion. The samples then examined for the degree of myometrial invasion based on medical record transvaginal USG data and compared it with the gold standard examination (histopathology).

Table 1. Demographic characteristics

Characteristics	n (%)
Age (mean ± SD)	53.37 ± 11.33
Menopausal age (mean ± SD)	50.14 ± 5.50
Parity status	
Nullipara	26 (31.7)
Primipara	14 (17)
Multipara	32 (39)
Grande multipara	10 (12.3)
Menopausal status	
Pre Menopause	36 (43.9)
Post Menopause	46 (56.1)
Contraception history	
Pill	7 (8.53)
Injection	3 (3.65)
IUD	8 (9.76)
Implant	0
Not using any contraceptive method	64 (78.06)

From 82 samples, endometrial cancer mostly found with myometrial invasion > 50% based on histopathology examination. There were 43 subjects (53,44%) with myometrial invasion > 50% and 23 (28,05%) with myometrial invasion < 50% and 16 (19,51%) with no myometrial invasion.

The most common type of endometrial cancer in the last 5 years in RSCM was endometrioid adenocarcinoma of 76 people (92.68%), the second most common type was clear cell carcinoma type which was found in 3 people (3.66%) and 3 other types with *Endometrial Stromal Sarcoma* (ESS) 2 people (2.45%), and 1 person squamous cell carcinoma (1.22%). In the endometrial type was found to be a type of mucinosa in 1 patient and, adenosquamous in 4 patients. Types of serous papillary carcinomas are not found in this study.

Based on the degree of differentiation of G1 as many as 31 people (37.8%), G2 as many as 33 people (40.24%), G3 as many as 13 people (15.85%) and five other respondents with an unknown degree of differentiation (6.1%).

Table 2. Histopathology Characteristic

Characteristics	n	(%)
Degree of Invasion		
Without Invasion	16	19.51
< 50%	23	28.05
>50%	43	52.44
Histopathology Type		
Endometrioid Adenocarcinoma	76	92.68
Papillary Serous Carcinoma	0	0
Clear Cell Carcinoma	3	3.66
Others		
Endometrial Stromal Sarcoma (ESS)	3	3.66
Squamous Cell Carcinoma	2	2.45
Degree of Differentiation	1	1.22
G1	31	37.80
G2	33	40.24
G3	13	15.85
Unknown (Gx)	5	6.10
Total	82	100

Based on table 2 the characteristics of histopathology examination results based on the depth of invasion in RSCM which found mostly was endometrial cancer with depth of invasion > 50% as much as 53.44% and patients with depth of invasion <50% as much as 28.05%, while there was without invasion as much as 19.51%. The type of endometrial cancer in the last 5 years at RSCM was the most 92.68% endometrioid adenocarcinoma type, the second type of clear cell type was 3.66% and the other 3 respondents were Endometrial Stromal Sarcoma (ESS) 2 people (2.45%), and 1 person squamous cell carcinoma (1.22%). Based on the degree of differentiation of G1 as many as 31 people (37.8%), G2 as many as 33 people (40.24%), G3 as many as 13 people (15.85%) and five other respondents unknown degree of differentiation (6.1%).

Table 3. Diagnostic Value of Transvaginal Ultrasound to determine the Presence of Myometrial Invasion in Endometrial Cancer cases

Ultrasound Degree of Invasion(pre-operative)	Histopathology Invasion (Postoperative)		
	Presence	Absence	Total
Presence	52	8	60
Absence	14	8	22
Total	66	16	82

Sensitivity	: 78.79 % (95% CI 66.98– 87.89%)
Specificity	: 50 % (95% CI 24.65 – 75.35 %)
Positive Predictive Value	: 86.67 % (95% CI 79.67– 91.51%)
Negative Predictive Value	: 36.36 % (95% CI 22.53 – 52.89 %)
Positive Possibility Ratio	: 1.58 (95% CI 0.95 – 2.61)
Negative Possibility Ratio	: 0.42 (95% CI 0.22 – 0.83)

Table 4. Diagnostic Value of Transvaginal Ultrasound in todetermine theDegree of Myometrial Invasion in Endometrial Cancer cases

The Degree of Invasion based on USG examination (Preoperative) (%)	Histopathology Invasion (Postoperative)		
	>50%	<50%	Total
>50	35	9	44
<50	8	30	38
Total	43	39	82

Sensitivity	: 81.40 % (95% CI 66.60– 91.61 %)
Specificity	: 76.92 % (95% CI 60.67 – 88.87 %)
Positive Predictive Value	: 79.55% (95% CI 68.30– 87.53%)
Negative Predictive Value	: 78.95 % (95% CI 66.23 – 87.76%)
Positive Possibility Ratio	: 3.53 (95%CI 1.95 – 6.37)
Negative Possibility Ratio	: 0.24 (95% CI 0.13 – 0.46)

DISCUSSION

This study managed to get a total of 82 subjects. Based on our medical records on patients who have radiation or chemotherapy outside, with other gynecological malignancies, or no hysterectomy before which was not included in this study because it may affect the result of examinations. For transvaginal ultrasound examinations used in this study is Voluson E8 with transvaginal probes EC4-9ES with 4-9 MHz frequency The result of ultrasound examinations in this study can be considered valid if the USG tools were calibrated every year and used by experts who are competent in their field.

Based on menopausal status, endometrial cancer more likely found in menopause age (56.1%) compared to premenopause (43.9%). Based on demographic data that we obtained in this study showed that the mean age of endometrial cancer diagnosis at RSCM was 53 years, and menopause means age was 50 years. When viewed based on menopausal status, endometrial cancer more common in menopausal age patient (56.1%) than pre-menopause (43.9%). We obtained menopausal age same as mean menopausal age based on BKKBN data in 2015 that is 50 years. This different from SOGC data in 2013, which only 10-15% cases of endometrial cancer are found at premenopause age. This difference may be due to we do not control the risk factor, such as BMI and lifestyle, history of patient illness that may be a risk factor for endometrial cancer such as PCOS.[3,4] Our data showed multiparous patient had more than nulliparas because we do not seek another risk factor in these multipara patients and for two to four parity grouped as multiparous.

Other demographic data on contraceptive use in accordance with studies that stated contraceptive use decreases estrogen exposure and increases progesterone levels in women and has a protection effect.[9,10]Most of endometrial cancer cases found in subjects without history of contraception used 78.06% and least in women with a family history of hormonal contraceptives (8.53% pill or injection 3.65%). This study did not seek further effects of these risk factors on the endometrial cancer incidence, but only provides an overview of the spread of risk factors.

Based on the cancer register study in the last five years at RSCM, most cases were invasive. There were 52.44% cases with the invasion to endometrium depth >50%, 28.04% cases with <50% endometrium invasion and 19.51% cases with no invasion. Although most cases are endometrioid types with slow progress than other types of endometrial cancers, most finding, in this case, involves more than 50% of invasion. Like wise, in the degree of differentiation, G1 is more commonly found with less than one third of invasion in the myometrium.10 This may be due to the late diagnosis of endometrial cancer, which may be influenced by factors that will not be discussed further.

Based on cancer type, the incidence of endometrial cancer type 1 or endometrioid estrogen dependent is in the first place (92.68%). The second most common type is the clear cell type of 3.66%. Based on this study, no serous papilosa type was found in endometrial cancer patients at RSCM in the last five years.

The data is slightly different from the study in Turkey who acquired the endometrioid type as much as 87%, while the other type that is found is papillary serosa carcinoma of 7% not found in the last five years study data at RSCM. In the previous study, the percentage of clear cell types was not much different from the data we got as much as 2%. Histopathological study data from 432 patients in the Netherlands in 2013 showed the highest non endometrioid type was 7.6% paposa serosa not found in RSCM, in which case the possibility of races affected the incidence of this cancer.[11] More than 85% of endometrial cancers are endometrioid types of estrogen dependent. Risk factors for this type are long-term estrogen exposures.[9] Long-term estrogen exposure is also consistent with the findings of most endometrial cancer at menopause as much as 56.10% compared with premenopause.[9]

Based on the data, the endometrioid type for G1, G2 and G3 are 26%, 28%, and 10% from all cases. There was no estrogen receptor with a high differentiated degree and advanced stage on clear cell type. This data was fit with this study,

which showed only G3 differentiation staging and undifferentiated cases. ESS incidence was 1% and based on the histopathogenesis, long exposure estrogen and PCOS can not be conclusive to define as a risk factor for ESS. Undifferentiated cases on this tumor were not based on mitosis phase but based on pleomorfism and core necrosis. This statement fits with ESS characteristics in another study which had 2 subjects with undifferentiated stage ESS (Gx). Most of the endometrioid cases were found with stage 1 and 2 differentiation which had a good prognosis.[12]

The main objective of this study is to obtain the diagnostic value of transvaginal ultrasonography and to obtain sensitivity, specificity, positive predictive value, the negative predictive value of transvaginal ultrasound are 78.79%, 50%, 86.67% and 36.36%. Most of the studies which we found, did not differentiate between invasive findings and less than half of myometrium because of the risk of lymph nodes involvement was considered to be the same and did not affect the staging and management.[13] However, in the case of no myometrial invasion there was no pelvic lymph node metastase, whereas in the case of myometrial invasion although less than one-third of myometrial thickness, there were 3-9% pelvic lymph node metastases.[9] In addition, it affects the incidence of distant metastases. In patients who did not undergo a myometrial invasion, only 4.3% whereas if the invasion was found <50% the depth of myometrium is 10-11%. In this case, invasion finding although <50% based on transvaginal ultrasound may be considered for screening for distant metastases and operator accuracy in assessing intraoperative lymph node spreading.

Transvaginal ultrasound in assessing the myometrial depth of invasion >50% has sensitivity, specificity, positive predictive value, negative predictive value, and accuracy 81.40%, 76.92%, 79.55%. moreover, 82.69%. Based on the meta-analysis in 2014, the sensitivity and specificity og transvaginal ultrasound in assessing the depth of invasion is 82% and 81%. The different diagnostic value may be due to fewer sample sizes or due to the differences of endometrial depth measurement techniques with transvaginal ultrasound in ultrasonogrpaher that is different from each other in this study and previous studies.[13]

Our study shows that ultrasound can be a screening tool to see the invasion, because of its good sensitivity, but insignificant in determining the stage and prognosis. Based on this result, the use of transvaginal ultrasound can not be the only option to select the extensive candidate of operative patients.

In using transvaginal ultrasound, it is necessary to note the risk factors, type, and stage of invasion to be a diagnostic tool in determining the next procedure and patient prognosis.

The use of transvaginal ultrasound in assessing the stage of invasion can be a good and efficient diagnostic tool in preoperative assessment. However, the assessment of depth of invasion can nto be sparated from the assessment of the type of cancer and degree of differentiation in determining stage and prognosis. The disadvantage of this study is the incompleteness of medical record that allows for exclusion criteria of circumstances that allow for the occurrence of a false negative number that will affect the sensitivity and false positive numbers that will affect the specificity number. The absence of control throughout the preoperative assessment of transvaginal ultrasound by operative hysterectomy became the weakness of this study. In addition, Kappa test control is not performed to see the equivalence of ultrasound operators, whereas ultrasound diagnostic tools are highly operator dependent.

CONCLUSION

The accuracy of transvaginal ultrasound obtained from this study is not much different from other studies conducted in other countries. However, in this study obtained ultrasound accuracy in assessing the depth of invasion of endometrial cancer is better than determining the presence or absence of invasion. In this case, transvaginal ultrasound can be used as an efficient diagnostic tool in determining the management and prognosis of endometrial cancer. Based on the invasion of the incidence of endometrial cancer with invasion>50% is the most found in RSCM in 2011-2016 as much as 52.44%. Based on the type of histopathology, the most incidence of endometrial cancer is endometrioid type as much as 92.68%. Based on the degree of differentiation of the incidence of endometrial cancer in RSCM is G2 of 40.24%.

This cross-sectional study with a limited sample needs to be considered for further research, especially by performing a transvaginal ultrasound equivalent examination in assessing invasion by the same expert to avoid any bias between examiners. Moreover, as a transvaginal ultrasound diagnostic tool in assessing the depth of invasion needs to be combined with findings of differentiation and cell type degrees to determine prognosis.

REFERENCES

1. Aziz MF. Gynecological cancer in Indonesia. J Gynecol Oncol. 2009;20: 8–10.
2. Dimitraki M, Tsikouras P, Bouchlariotou S, Dafopoulos A, Liberis V, Maroulis G, et al. Clinical evaluation of women with PMB. Is it always necessary an endometrial biopsy to be performed? A review of the literature. Arch Gynecol Obstet. 2011;283(2):261–6.
3. Alcázar JL, Galván R, Albela S, Martinez S, Pahisa J, Jurado M, et al. Assessing Myometrial Infiltration by Endometrial Cancer: Uterine Virtual Navigation with Three-dimensional US. Radiology [Internet]. 2009;250(3):776–83. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2503080877
4. Richter HE, R. Edward Varner. Berek & Novak's Gynecology, 14th. Berek & Novak's Gynecology, 14th Ed. 2007:469–80.
5. Torricelli P, Ferraresi S, Fiocchi F, Ligabue G, Jasonni VM, Di Monte I, et al. 3-T MRI in the preoperative evaluation of depth of myometrial infiltration in endometrial cancer. Am J Roentgenol. 2008;190(2):489–95.
6. Berretta R, Merisio C, Piantelli G, Rolla M, Giordano G, Melpignano M, et al. Preoperative transvaginal ultrasonography and intraoperative gross examination for assessing myometrial invasion by endometrial cancer. J Ultrasound Med. 2008;27(3):349–55.
7. Beddy P, Moyle P, Kataoka M, Yamamoto AK, Joubert I, Lomas D, et al. Evaluation of depth of myometrial invasion and overall staging in endometrial cancer: comparison of diffusion-weighted and dynamic contrast-enhanced MR imaging. Radiol [Internet]. 2012;262(2):530–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22114239
8. Takac I. Transvaginal ultrasonography with and without saline infusion in assessment of myometrial invasion of endometrial cancer. J Ultrasound Med. 2007;26(7):949-955-957.
9. Berek, Jonathan S.; Hacker N. Berek and Hacker's Gynecologic Oncology. In: Berek, Jonathan S.; Hacker NF, editor. Berek and Hacker's Gynecologic Oncology, 5th Ed. 5th ed. Lippincott Williams & Wilkins; 210AD: 410.
10. Group C, Cancer E. Endometrial cancer and oral contraceptives : an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol [Internet]. 2015;2045(15):1–10. Available from: http://dx.doi.org/10.1016/S1470-2045(15)00212-0
11. Visser NCM, Bulten J, van der Wurff AAM, Boss EA, Bronkhorst CM, Feijen HWH, et al. PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, pre-operative recognition of high risk endometrial carcinoma: a multicentre prospective cohort study. BMC Cancer . 2015;15:487.
12. Puliyath G, Nair MK. Endometrial stromal sarcoma: A review of the literature. Indian J Med Pediatr Oncol. 2012;33(1):1–6.
13. Akbayir O, Corbacioglu A, Numanoglu C, Guleroglu FY, Ulker V, Akyol A, et al. Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. Gynecol Oncol. 2011;122(3):600–3. Available from: http://dx.doi.org/10.1016/j.ygyno.2011.05.041

Research Article

Pap Smear Cytology Results in Patients Under Visual Inspection of Acetic Acid (VIA) in Primary Health Care Centre

Hasil Sitologi Pap Smear pada Pasien di Bawah Inspeksi Visual Asam Asetat (IVA) di Pusat Perawatan Kesehatan Utama

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Abstract

Objective : : We compared the results of Pap Smear and VIA in Primary Healthcare Centres (PHCs).

Methods : This was a descriptive study that investigated Pap smear cytology results in patients who underwent visual inspection of acetic acid in PHC for early detection of cervical cancer. This research was done in three PHCs (Tikala Baru, Tuminting and Paniki), which appointed by Manado Health Department as they have certified general practitioner, midwives, and nurse for VIA examination. The Pap smear examination was performed by researchers and VIA performed by certified PHC VIA Team using tools, equipment, available at the PHCs without intervention.

Results : Of 55 subjects, 15 and 40 subjects were VIA positive and negative, respectively. Fifteen samples with positive VIA there were only three subjects with dysplasia (LSIL) results in Pap smear, and 40 samples with VIA negative there were two samples with dysplasia (LSIL) results in Pap smear.

Conclusions : The result of VIA examination in primary health care with VIA positive was only 20% had dysplasia (LSIL) on pap smears, and negative VIA sample was 5% with dysplasia (LSIL) on Pap smear.

Keywords : cervical cancer, pap smear, VIA

Abstrak

Tujuan : *Membandingkan hasil pemeriksaan gambaran sitologi Pap Smear dengan hasilpemeriksaan IVA di Puskesmas.*

Metode : *Penelitian ini merupakan penelitian deskriptif untuk mengetahui hasil sitologi Pap Smear pada pasien yang telah dilakukan pemeriksaan inspeksi visual asam asetat di fasilitas kesehatan tingkat I untuk deteksi dini kanker serviks. Penelitian ini dilakukan di tiga Puskesmas (Puskesmas Tikala Baru, Tuminting, dan Paniki) yang telah diberikan pelatihan IVA yang ditunjuk oleh Dinas Kesehatan Kota Manado. Pemeriksaan Pap Smear dilakukan oleh penelitidan IVA dilakukan oleh petugas kesehatan tingkat I dengan menggunakan alat, perlengkapan, yang tersedia di Puskesmas tanpa intervensi.*

Hasil : *Dari 55 subyek, didapatkan 15 subyek dengan IVA positif, dan 40 subyek dengan IVA negatif. Dari 15 subyek dengan IVA positif hanya terdapat 3 orang diantara dengan hasil displasia pada Pap Smear, dan 40 subyek dengan IVA negatif terdapat 2 orang dengan hasil displasia pada Pap Smear.*

Kesimpulan : *Hasil pemeriksaan IVA di fasilitas kesehatan tingkat I dengan IVA positif hanya 20% memliki gambaran displasia (LSIL) pada hasil Pap smear dan sampel dengan IVA negative terdapat 5% dengan gambaran displasia (LSIL) pada hasil Pap Smear.*

Kata kunci : *IVA, kanker serviks, pap smear*

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INTRODUCTION

Visual inspection of the cervix with acetic acid (VIA) was a program that Indonesia's Ministry of Health begins from 2015 until 2019 in order to run a project called "Prevention and Early Detection of Cancer in Woman". The objective of this project is to decrease the morbidity and mortality of breast cancer and cervical cancer as the leading cause of cancer among woman. Hopefully, this program will help to increase early detection for precancerous lesions in cervical cancer. Visual inspection of the cervix with acetic acid (VIA) is an effective, immediate, inexpensive screening test that can be done in PHCs and provided by trained health workers such as midwife and general practitioner.[1]

In order to make this cervical cancer prevention more effective and well treated, WHO using a particular approach to administer the screening of precancerous lesion of cervical cancer. Respectively, VIA and conventional Pap smear which is the recommended screening to this program had their advantages and disadvantages.[2]

Cervical cancer is the second most common cancer in Indonesia with an incidence of approximately 12,7%. Today, Indonesia's Health Department estimated about 90-100 new cases per 100.000 cases of cervical cancer. According to GLOBOCAN 2012, cervical cancer is the third most common cancer in woman worldwide and the fifth most common cancer globally.[3]

Cervical cancer is the most common malignancy in women. Moreover, it is responsible for 85% death among women in developed countries. For over than 70 years, Cervical intraepithelial neoplasia had been known as an early phase of cancer; therefore if an effective screening and treatment are well-implemented, this program will decrease the incidence and mortality of cervical cancer significantly. However, the standard strategy to prevent cervical cancer as known as cervical cytology, HPV (Human Papilloma Virus) test, and colposcopy cannot be done in developed countries because of economic problem and other infrastructure problem. An effective screening strategy is tough to achieve a conclusion because of the difference between the availability of health resource and health problem among each country. However, we have to find a solution for cervical cancer screening in health service systems where cytology-based screening and colposcopy are not feasible. Clinical approach and testing of cervical cancer screening are necessary.[4-7]

Globally, the rate of cervical cancer is 12%, and cervical cancer became the fourth most common cancer after breast cancer, lung cancer and colon cancer. In developed countries, cervical cancer is the most common female cancer. In fact, it occurs in more than 85% of women.[4,5]

METHODS

This study is a descriptive study to find out Pap smear cytology results in patients who have performed visual inspection of acetic acid in PHC for early detection of cervical cancer. This research was done in 3 PHCs (Tikala Baru, Tuminting and Paniki), which appointed by Manado Health Department because they have certified general practitioner, nurse, and midwives for VIA examination. The Pap smear examination was performed by researchers and VIA performed by certified paramedics using tools, equipment, available at the PHC without intervention.

The Pap smear examination was performed by researchers first and continue VIA performed by certified paramedics.

RESULTS

We recruited 55 subjects. There were 15, 5, and two subjects with VIA positive, Pap smear with LSIL (3 women with VIA positive, two women with VIA negative).

Table 1. Distribution of Number of Subjects and Results of Examination Based on PHC.

Examination	Primary Healthcare Centre					
	Tikala Baru		Tuminting		Paniki	
	n	%	n	%	n	%
VIA						
Positive	13	52	2	9.52	0	0
Negative	12	48	19	90.48	9	100
Total	25	100	21	100	9	100
Pap Smear						
Dysplasia	4	16	1	4.76	0	0
Normal	21	84	20	95.24	9	100
Total	25	100	21	100	9	100
Total Samples	25	45.45	21	38.18	9	16.37

The number of 55 women came from 3 PHCs, Tikala PHC has the highest number of 25 women (45.45%), with the highest number of VIA Positive 13 (52%) women, and the number of Pap smears with the highest number of dysplasia four women (16%).

Table 2. Distribution of VIA Observer at Puskesmas

Primary Health Care	Observer		
	Doctor	Midwife	Nurse
TikalaBaru	0	1	1
Tuminting	1	2	0
Paniki	0	1	0
Total	1	4	1

Distribution of health personnel trained to perform VIA in PHC consists of doctors, midwives or nurses. Most of the trained health workers from these 3 PHCs are midwives who have been trained.

Table 3. Overview of VIA Examination Results with Pap Smear.

VIA	Pap's Smear			Total
	LSIL	HSIL	Normal	
Positive	3	0	12	15
Negative	2	0	38	40
Total	5	0	50	55

Table 4. Comparison of VIA Examination Results with Dysplasia on the Pap Smear Results.

VIA	Pap's Smear		Total
	Dysplasia	Normal	
Positive	3	12	15
Negative	2	38	40
Total	5	50	55

From 55 samples, 15 patients with VIA positive and 40 VIA negative results. From 15 women with VIA positive results obtained 3 LSIL (dysplasia) from pap smears test. In women with negative VIA 2 women were found with LSIL (dysplasia) results. No HSIL result was found.

DISCUSSION

This study is held in three primary health care that appointed by Manado Department of Health; those are primary health care Tikala aru, primary health care Tuminting, and primary health care Paniki. Those primary health care are already trained some health worker to build a team to do the VIA test. In this study, the VIA test is examined by one doctor, one nurse and four midwives. The instruments and the schedule for the VIA examination are available in every single primary health care. Even cryotherapy is available in primary health care in Tikala Baru.

In this study, to get the adequate and valid result, Pap Smear is done by researchers and examined in anatomy pathology laboratory by anatomical pathology specialist. Based on some study that had been done in some other place, there should be no significant difference between the result of VIA test and Pap smear; however, a direct biopsy is the "Gold standard" examination.[8,9]

In this research (Table 1) 25 (45.5%) samples are taken from PHC in Tikala Baru, with VIA positive result, 13 (52%) women. From 13 women with VIA positive, we found three women with LSIL in Pap smear examination. Moreover, we found one patient with LSIL (Pap smear result) from the 13 patients with VIA negative. There is 21 (38.18%) research subject in PHC Tuminting. We found 2 (9.52%) patients with VIA positive result, and after the Pap smear examination, there is no LSIL and HSIL. We found one patient with LSIL from 19 patients with VIA negative. The examination of 9 research subject in PHC in Paniki, we found a VIA negative and no abnormalities in Pap smear examination. This result indicates that we will still found false positive if we use Pap Smear results as the reference. Every PHC will show the number of different false positive depends on the examiner.[9,10]

From the data above, every PHC got many false positive if Pap smear used as a reference, all kind of examination above is done by trained health personnel in each PHC. The results of this research (Table 1.2.) the number of examiners from 3 PHC are six persons consisting of one doctor, four midwives and one nurse. According to 5 years research that ministry of health held with JHPIEGO, not always VIA test result is confirmed by the doctor nor assumed that doctor is more accurate than midwife in PHC in Indonesia. From time to time, the result of the research will be more accurate. So that, the examination of VIA test should have an adequate accuracy because the personnel healthcare is already trained.[10]

The treatment of VIA-positive in primary health care in Manado is cryotherapy procedure to those who fulfill the terms and condition. Every patient with VIA positive will go through the counselling to be informed about the cryotherapy procedure. Cryotherapy does not perform immediately in one day, cause the procedure need preparation such as the availability of CO2, informed consent from

husband or family and the lack of trained doctor/ medical specialist to perform the cryotherapy procedure so that we need to arrange the schedule for the procedure. Before performing the cryotherapy procedure, the VIA test is repeated by a certified general practitioner/medical specialist, different knowledge and experience between the health worker will cause a negative result or did not fulfill the terms and condition of cryotherapy. Therefore the confirmation by a certified general practitioner/medical specialist is a necessary thing to reduce the number of false positive in primary health care.[1,10]

There have been many studies that consist the comparison between the accuracy, sensitivity, and specificity of VIA test and Pap smear and the result is those two tests had no significant difference, for example, a meta-analysis conducted by Mustafa et al 2016, obtained that VIA test with 77% sensitivity, 82% specificity and Pap Smear sensitivity 84%, specificity 88%. In this study, 15 women with VIA positive only three women with Pap Smear result is LSIL. If Pap smear cytology examination which is performed by anatomical pathology specialist is used as a reference, then it shows very high false positives on VIA examination conducted by primary health care. The examination at primary health care will still be re-visualized before cryotherapy. Hopefully, the accuracy level in this VIA examination will get better eventually. However, the problem of the patients with VIA negative is there are two patients with LSIL cytology results. Eventually, this patient will pass the screening examination. Therefore it is necessary to look for factors that can decrease the accuracy level of VIA examination in Primary health care.[8,10]

The outcome of VIA test and Pap smear examination is those examinations should not have a significant difference, there will be some factors that need to be evaluated furthermore to increase the accuracy of VIA test. All VIA examinations procedure in this study is done by a health worker at primary health care, using the sites, materials, and equipment that is available at the public centre of health. Some of the factors that can induce false positives, including a light source, inflammation, infection, metaplasia, acetic acid concentrations, and the ability of the ace to white assessment to the examiner.[10,11]

The ability of VIA assessments by health workers is related to training and experience in conducting VIA. Examination of VIA conducted by primary health care before cryotherapy will be confirmed again by doctor/specialist of cryotherapy. According to research on "Cervical and Breast Cancer Prevention" (CECAP) program in collaboration with JHPIEGO which is a research to get the pattern or model in the current VIA program, the false rate in the positive VIA reaches 70.6% in the first 6 months, and after approaching 5 years decrease to 20.3%. Therefore, using only the training as the main learning is not enough, every trained health worker needs to be guided and assisted so that the level of sensitivity and specificity will be better.[10]

The targeted number of risk women in Manado who need screening is 64.214 women, in 2017, only 3% of the women underwent VIA test. Therefore, the PHC became the first to be the early detection of cervical cancer with a simple, inexpensive and immediate VIA examination.

CONCLUSION

Based on research result from 3 primary health care (Tikala Baru, Tuminting, and Paniki) in 55 women, the research subjects obtained VIA positive 15 samples (27.27%) and negative 40 samples (72.73%).

VIA test that conducted at primary health care and Pap smear in this study still has a difference in outcome, with 15 persons with VIA positive only 3 (20%) having dysplasia features in the Pap smear, and in 40 individuals with VIA - negative patients, there were 2 (5%) patients with dysplasia on the Pap Smear.

If the Pap smear is the reference/standard, there should be an evaluation and additional training for certified health personnel for VIA examination at primary health care. Research using direct biopsy using colposcopy as a gold standard needs to be done to evaluate the results of VIA examination at PHC in Manado. Research with more samples to assess sensitivity, specificity, and accuracy VIA examination in Manado needs to be done to obtain better validity.

REFERENCES

1. KemKes RI. Program Nasional Gerakan Pencegahan dan Deteksi Dini Kanker Leher Rahim dan Kanker Payudara. 2015:4-6.
2. WHO. Comprehensive cervical cancer control: A guide to essential practice. Geneva, Switzerland: WHO; 2014:119-47.
3. Andrijono GP. Panduan Penatalaksanaan Kanker Serviks: Kementerian Kesehatan RI; 2017. Available from: http://kanker.kemkes.go.id/guidelines/.
4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
5. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133-45.
6. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999;318(7188):904-8.
7. Willoughby BJ, Faulkner K, Stamp EC, Whitaker CJ. A descriptive study of the decline in cervical screening coverage rates in the North East and Yorkshire and the Humber regions of the UK from 1995 to 2005. J Public Health (Oxf). 2006;28(4):355-60.
8. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet. 2016;132(3):259-65.
9. Blumenthal PD MN. JHPIEGO's cervical cancer prevention learning resource package. Johns Hopkins University, USA: Jhpiego; 2007:8-10.
10. Kim YM, Lambe FM, Soetikno D, Wysong M, Tergas AI, Rajbhandari P, et al. Evaluation of a 5-year cervical cancer prevention project in Indonesia: opportunities, issues, and challenges. J Obstet Gynaecol Res. 2013;39(6):1190-9.
11. Pothisuwan M, Pataradool K, Tangjitgamol S, Srijaipracharoen S, Manusirivithaya S, Thawaramorn T. Visual inspection with acetic acid for detection of high-grade lesion in atypical squamous cells and low grade squamous intraepithelial lesions from cervical Pap smear. J Gynecol Oncol. 2011;22(3):145-51.

Research Article

HE4 Levels in Ovarian Cancer-Resistant Menopausal Women

Kadar HE4 pada Perempuan Menopause yang Resisten Kanker Ovarium

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Abstract

Objective : To analyse the predictive value of HE4 in ovarian cancer patients according to their resistance and menopausal status.

Methods : Thirteen premenopausal and twenty-five menopausal ovarian cancer patients were measured for HE4 levels measured using automated chemiluminescent microparticle immunoassay ARCHITECT HE4. Patients categorized into resistant and non-resistant after six cycles of chemotherapy in addition to their clinical symptoms and ultrasound image of cancer.

Results : The mean HE4 levels were higher in the resistant group compared with a non-resistant group (274.97 pmol/l vs 128.83 pmol/l; p=0.015). Five menopausal resistant women with HE4 levels >140 pmol/l compared with two women in the non-resistant group. In the pre-menopause group, eight resistant women with HE level >70 pmol/l whereas four women in the non-resistant group. HE levels in menopausal and premenopausal for both ovarian cancers resistant and non-resistant were not significantly different (p>0.05).

Conclusions : HE4 levels in resistant ovarian cancer patients are higher compared with non-resistant but do not predict ovarian cancer resistance based on patient menopausal status.

Keywords : HE4, ovarian cancer, resistance.

Abstrak

Tujuan : *Untuk menganalisis nilai prediktif HE4 pada pasien kanker ovarium berdasarkan resistensi dan status menopausenya.*

Metode : *Dilakukan pengukuran kadar HE4 menggunakan metode microparticle immunoassay ARCHITECT HE4 terhadap pasien kanker ovarium terdiri atas 13 perempuan premenopausal dan 25 perempuan menopause. Pasien dikategorikan menjadi resisten dan tidak resisten setelah 6 siklus kemoterapi selain gejala klinis dan gambar USG.*

Hasil : *Rerata kadar HE4 rata-rata lebih tinggi pada kelompok yang resisten dibandingkan dengan kelompok yang tidak resisten (274,97 pmol/l vs 128,83 pmol/l; p=0,015). Terdapat 5 perempuan menopause yang resisten kanker ovarium dan 2 perempuan dalam kelompok yang tidak resisten dengan kadar HE4 >140 pmol/l. Pada kelompok premenopause, 8 perempuan yang resisten dengan tingkat HE >70 pmol/l sedangkan 4 perempuan dalam kelompok tidak resisten. Kadar HE dalam menopause dan premenopause untuk kedua kanker ovarium resisten dan tidak resisten tidak berbeda secara signifikan (p>0,05).*

Kesimpulan : *Kadar HE4 pada pasien kanker ovarium lebih tinggi daripada tidak resisten tetapi tidak memprediksi resistensi kanker ovarium berdasarkan status menopause pasien.*

Kata kunci : *HE4, kanker ovarium, resistensi .*

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INTRODUCTION

Ovarian cancer is the fifth leading cause of death in women.[1] Most ovarian cancer patients are diagnosed at an advanced stage (FIGO stage III-IV); hence, the 5-year survival rate in ovarian cancer depends on the stage, at early stage of ovarian cancer survival rate of about 80-90% while in advanced stage it is only about 30%.[2] Despite advances in treatment, the survival rate remains unchanged. Therefore, an understanding of the pathogenesis of ovarian neoplasm molecules is needed so that new therapeutic targets or biomarkers for early detection of ovarian cancer or ovarian neoplasm can be identified and improved the treatment outcomes.[3]

Cancer antigen 125 (CA125) is mostly used as a serological biomarker in routinely for managing patients with gynecologic cancer[4] but limited due to its sensitivity and specificity. Human epididymis protein-4 (HE4) is a new promising marker

that over expressed in healthy tissue and ovarian cancer.[5] Its expression does not depend on CA125.[6] Serum HE4 is more specific than CA125 in differentiating tumors malignancy.[7]The serum HE4 level may have prognostic value for evaluating treatment response, including chemoresistance. The objective of this study is to analyse the predictive value of HE4 in ovarian cancer patients according to their resistance and menopausal status.

METHODS

Ovarian cancer patients, premenopausal and menopausal, were enrolled in a cross-sectional study was conducted at affiliated hospitals of the Obstetrics and Gynecology Department of Universitas Hasanuddin, Makassar, South Sulawesi. Patients were categorized as resistant and non-resistant after six cycles of chemotherapy in addition to their clinical symptoms and ultrasound image of cancer. HE4 levels measured using automated chemiluminescent microparticle immunoassay ARCHITECT HE4 (Fujirebio Diagnostics, Abbott's, UK) according to the manufacturer's instruction. Mann Whitney test used to compare mean HE4 levels between resistant and non-resistant patients. A *p*-value <.05 was considered statistically significant. Written informed consent obtained from all pregnant women and the Health Research Ethics Committee Faculty of Medicine Universitas Hasanuddin Makassar approved the study.

RESULTS

Table 1 shows patients at the age of menopause was 28(73.7%) women, and in 10 (26.3%) women were premenopausal, 23(60.6%) women were multiparous, 24(63.2%) women not using any methods of contraception, and 33(86.8%) were married. Histological findings show the type of ovarian cancer consisted of serous (63.2%) and mucinous (35.8%) with 78.9% of patients in advanced FIGO stage (III-IV).

A significant difference in HE4 levels between resistant and non-resistant ovarian cancer show in table 2. The mean HE4 levels were higher in the resistant group compared with a non-resistant group (274.97 pmol/l vs 128.83 pmol/l; p = 0.015). Five menopausal resistant women with HE4 levels >140 pmol/l compared with two women in the non-resistant group. In the pre-menopause group, eight resistant women with HE level >70 pmol/l whereas four women in the non-resistant group. HE levels in menopausal and premenopausal for both ovarian cancers resistant and non-resistant were not significantly different ($p>0.05$).

Table 1. Demographic Characteristics

Characteristics	n	%
Age		
Premenopausal	13	34.2
Menopausal	25	65.8
Parity		
Nulliparous	8	21.1
Primipaous	4	10.5
Multiparous	26	68.4
Contraceptive methods		
Pills	3	7.9
DMPA	10	26.3
IUD	1	2.6
None	24	63.2
Marital status		
Married	33	86.8
Not married	5	13.2
Histology		
Serous	24	63.2
Mucinous	14	36.8
FIGO stage		
I-II	8	21.1
III-IV	30	78.9

Table 2. HE4 Level Based on Ovarian Cancer Resistance

HE4 level (pmol/l)	Resistant (n=19) n%	Non-resistant (n=19) n%	*P-value*	RR	95%CI
Mean	274.97	128.83	0.015	-	214-259
Menopause					
>140	5(71.4)	2(28.6)	0.085	2.143	0.954-4.788
≤140	6(33.3)	12(66.7)			
Pre-menopausal					
>70	8(66.7)	4(33.3)	0.385	0.33	0.150-0.742
≤70	0	1(100)			

DISCUSSION

Our study shows that the mean HE4 levels in women with ovarian cancer resistant at menopausal age were higher compared with women with premenopausal non-resistant ovarian cancer. Similar to our findings, the previous study that shows the mean HE4 plasma in women with ovarian cancer was 225.83 pmol/l. Post therapy, 91.3% of resistant ovarian cancer patients had elevated HE4 levels up to 2-fold compared with HE4 levels before therapy.[8] Because the mean age of our study was women in the menopausal period, the HE4 levels found in women non-resistant ovarian cancer were different from findings of the previous studies.

HE4 levels are affected by age. Urban et al recommend the use of age-based thresholds per decade to achieve 95% HE4 specificity. The proposed threshold range is 41.4 pmol/l μm for women aged 30 years to 82.1 pmol/l for women aged 80 years.[9] Urban In addition to age, HE4 levels are also affected by pregnancy. During pregnancy, HE4 levels decreased compared with non-pregnant premenopausal women. Women with late menarche and smoking have higher HE4 levels. While the menstrual cycle, endometriosis, use of contraceptives containing estrogen and progestin does not alter serum HE4 levels.[10]

Our study also found no significant association between HE4 levels and ovarian carcinoma resistance in premenopausal patients. However, a review in 28 clinical studies found that HE4 levels decreased immediately after therapy but again increased when recurrence occurred. Failure of HE4 levels to return to normal levels after administration of therapy indicates a poorer prognosis. When comparing four markers, including CA 125, HE4, MMP-7, and mesothelin were monitored in patients with advanced-stage ovarian cancer after surgery and chemotherapy, HE4 levels increased in 4.5 months of recurrence. In patients with elevated levels of CA 125, HE4 levels have increased before CA125 elevated. In patients with negative recurrence according to CA 125 levels and imaging show, HE4 levels were higher than the cut-off value.[11]

HE4 has been known to trigger migration and adhesion of ovarian cancer cells. In an in vitro study, HE4 knockdown leads to inhibition of tumor growth. HE4 overexpression in endometrial cancer cell lines induces in vivo and in vitro cell proliferation. These findings support the role of HE4 in tumor progression. HE4 act as a protease inhibitor, decreasing serene protease activity Prss35 and Prss23, which degraded type I collagen accumulating in renal fibrosis. Fibrosis was inhibited by three mouse models when given HE4 neutralizing antibodies. [12] these findings suggest that HE4 potentially as a therapeutic target in renal fibrosis. HE4 also has an additional role in maintaining innate immunity.

Published the first prospective controlled study evaluating the sensitivity and specificity of HE4 in detecting resistant ovarian cancer. From 68 patients with ovarian cancer, the sensitivity and specificity of HE4 in predicting resistant ovarian cancer with a cut-off 70 pmol/l were 73% and 100%, respectively.[13] Prospectively enrolled 73 patients with resistant ovarian cancer and found that HE4 level 250 pmol/l as the cut-off had 52% sensitivity and 93.8% specificity in predicting disease resistance.[14] Another study suggests HE4 has prognostic value in ovarian cancer resistance with a superior sensitivity compared to CA125 (91.3% vs 52.7%, respectively).[8] HE4 had a sensitivity of 96.9% in another study.[15]

In our study, the sensitivity and the specificity was 73.68% and 68.2% according to a cut-off of 140 pmol/l as the mean HE4 levels in all women with ovarian cancer resistant in menopausal. This value means that HE4 levels can be relied upon to detect the risk of ovarian cancer resistant. The difference in specificity and sensitivity of some previous studies may be due to the difference in cut-off used in the study. In previous studies, HE4 has a high specificity and sensitivity in menopausal ovarian cancer.[16] Higher sensitivity and specificity (98% and 100%, respectively) of HE4 compared with CA125 between normal women and women with pelvic mass due to gynecologic cancer (cancer (ovarian, endometrial, cervical).[17] ROMA's prediction of sensitivity to ovarian cancer was higher in menopause compared with premenopausal with 94% sensitivity and 75% specificity.[18]

Despite the progress of ovarian cancer treatment, most patients will recur after a complete clinical response and most patients is incurable. As a result, treatment of resistant

is an essential aspect of the overall management of epithelial ovarian cancer. In epithelial ovarian cancer resistant, HE4 levels increase significantly in patients receiving platinum-based adjuvant chemotherapy.[19] Introducing HE4 as a new marker for predicting platinum-sensitivity and interval optimal cytoreduction is promising.[20]

Although this study showed no association between HE4 levels and the risk of resistant ovarian cancer, the results of the study should be interpreted with caution due to the limitations of our study. The first is a relatively small sample size so that the results of this study may be influenced by chance. Although we have controlled confounding variables with exclusions, other confounding variables such as clinical stage, degree, CA125 level, and post-chemotherapy disease residue were not analyzed.

CONCLUSION

In conclusion, HE4 levels in resistant ovarian cancer patients are higher compared with non-resistant but do not predict ovarian cancer resistance based on patients menopausal status.

REFERENCES

1. Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 2004;291(22):2705-12.
2. Reich R, Hadar S, Davidson B. Expression and clinical role of protein of regenerating liver (PRL) phosphatases in ovarian carcinoma. Int J Mol Sci. 2011;12(2):1133-45.
3. Schwartz DR, Kardia SL, Shedden KA, Kuick R, Michailidis G, et al. Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. Cancer Res. 2002;62(16):4722-9.
4. Lee KR, Tavassoli FA, Prat J, Dietel M, Gersell DJ, Karselatze AI, Hauptmann S, Rutgers J. WHO histological of tumours of the ovary (chapter 2). In: Tassoli FA, Decilee O, editors. In pathology and genetics of tumours of the breast and female genital organs. Lyon: IARC Press; 2003:1113–61.
5. Galgano MT, Hampton GM, Frierson HF Jr. Comprehensive analysis of HE4 expression in normal and malignant human tissues. Mod Pathol. 2006;19:847Y853.
6. Steffensen KD, Waldstrom M, Brandslund I, Jakobsen A. Prognostic impact of prechemotherapy serum levels of HER2, CA125, and HE4 in ovarian cancer patients. Int J Gynecol Cancer. 2011;21:1040–7.
7. Escudero JM, Auge JM, Filella X, Torne A, Pahisa J, Milna R. Comparison of serum human epididymis protein 4 with cancer antigen 125 as a tumor marker in patients with malignant and nonmalignant diseases. Clin Chem. 2011;57:1534–44.
8. Innao P, Pothisuwan M, Pengsa P.Does Human Epididymis Protein 4 (HE4) Have a Role in Prediction of Recurrent Epithelial Ovarian Cancer. Asian Pac J Cancer Prev. 2016;17(9):4483-6.
9. Urban N, Thorpe J, Karlan BY, McIntosh MW, Palomares MR, et al. Interpretation of single and serial measures of HE4 and CA125 in asymptomatic women at high risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2012;21(11):2087-94.
10. Simmons AR, Baggerly K, Bast RC Jr. The emerging role of HE4 in the evaluation of epithelial ovarian and endometrial carcinomas. Oncology (Williston Park). 2013;27(6):548-56.
11. Piovano E, Attamante L, Macchi C, Cavallero C, Romagnolo C, et al. The role of HE4 in ovarian cancer follow-up: a review. Int J Gynecol Cancer. 2014;24(8):1359-65.
12. LeBleu VS, Teng Y, O'Connell JT, Charytan D, Müller GA, et al. Identification of Human Epididymis Protein-4 as a Novel Fibroblast-Derived Mediator of Fibrosis. Nat Med. 2013; 19(2): 227–31.
13. Plotti F, Capriglione S, Terranova C, Montera R, Aloisi A, et al. Does HE4 have a role as a biomarker in the recurrence of ovarian cancer? Tumour Biol. 2012;33(6):2117-23.
14. Braicu EI, Fotopoulou C, Van Gorp T, Richter R, Chekerov R, Hall C, et al. Preoperative HE4 expression in plasma predicts surgical outcome in primary ovarian cancer patients: results from the OVCAD study. Gynecol Oncol. 2013;128(2):245–51.
15. Anastasi E, Marchei GG, Viggiani V, Gennarini G, Frati L, Reale MG. HE4: a new potential early biomarker for the recurrence of ovarian cancer. Tumour Biol. 2010;31(2):113-9.
16. Wei S, Li H, Zhang B. The diagnostic value of serum HE4 and CA-125 and ROMA index in ovarian cancer. Biomed Rep. 2016; 5(1): 41–4.
17. Montagnana M, Lippi G, Ruzzenente O, Bresciani V, Danese E, et al. The utility of human serum epididymis protein 4 (HE4) in patients with a pelvic mass. J Clin Lab Anal. 2009;23(5):331-5.
18. Terlikowska KM, Dobrzycka B, Witkowska AM, Mackowiak-Matejczyk B, Sledziewski TK, et al. Preoperative HE4, CA125 and ROMA in the differential diagnosis of benign and malignant adnexal masses. J Ovarian Res. 2016;9(1):43.
19. Zhu L, Zhuang H, Wang H, Tan M, Schwab CL, et al. Overexpression of HE4 (human epididymis protein 4) enhances proliferation, invasion and metastasis of ovarian cancer. Oncotarget. 2016;7(1):729-44.
20. Pelissier A, Roulot A, Guéry B, Bonneau C, Bellet D, Rouzier R. Serum CA125 and HE4 levels as predictors for optimal interval surgery and platinum sensitivity after neoadjuvant platinum-based chemotherapy in patients with advanced epithelial ovarian cancer. J Ovarian Res. 2016;9(1):61.

Research Article

The Accuracy of Modified Risk of Malignancy Index (RMI) in Predicting Malignancy of Epithelial Type Ovarian Tumor

Akurasi Modifikasi Risk of Malignancy Index dalam Memprediksi Keganasan Tumor Ovarium Tipe Epitel

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Abstract

Objective : To investigate the accuracy of modified Risk of Malignancy Index (RMI) in predicting malignancy of epithelial type ovarian tumour.

Methods : This research was comparative research using cross-sectional study design, which compared RMI modification and RMI method in predicting malignancy of epithelial type ovarian tumour. The sampling technique was consecutive sampling. This research was conducted on October 2017 until samples were fulfilled in Obstetrics and Gynecology Division of RSUP Dr. M. Djamil and Laboratory of RSUP Dr. M Djamil in Padang. Chi-square test was used to compare specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR, and accuracy of RMI modification and RMI with 95% CI (p≤0,05).

Results : A total of 61 subjects were recruited in this study. Sensitivity, specificity, PPV, NPV, PLR, NLR, and accuracy RMI modification scoring was 90.5%, 82.5%, 73.1%, 94.3%, 5.1, 0.1, dan 85.2%. Sensitivity, specificity, PPV, NPV, PLR, NLR, and accuracy RMI scoring was 66.7%, 70%, 53.8%, 80%, 2.2, 0.4, and 70%.

Conclusions : Modified RMI scoring method was more accurate in predicting the malignancy of ovarian type epithelial tumours than RMI.

Keywords : CA125, malignancy, ovarian tumor,pelvic mass, RMI.

Abstrak

Tujuan : *Mengetahui akurasi Risk of Malignancy Index (RMI) dalam prediksi keganasan tumor ovarium tipe epitel.*

Metode : *Penelitian ini merupakan penelitian komparatif dengan desain penelitian potong lintang yang membandingkan metode RMI modifikasi dan RMI dalam prediksi keganasan tumor ovarium tipe epitel. Jumlah sampel sebanyak 61 orang. Teknik pengambilan sampel berurutan. Penelitian di mulai pada bulan Oktober 2017 hingga jumlah sampel terpenuhi di Departemen Obstetri dan Ginekologi RSUP Dr. M Djamil dan Laboratorium RSUP Dr. M Djamil Padang. Untuk membandingkan spesifisitas, sensitivitas, nilai duga positif (NDP), nilai duga negatif (NDN), rasio kemungkinan positif (RKP), rasio kemungkinan negatif (RKN), dan akurasi RMI modifikasi dan RMI digunakan uji chi-square dengan 99% CI (p≤0,01).*

Hasil : *Sensitivitas, spesifisitas, NDP, NDN, RKP, RKN, dan akurasi skoring RMI modifikasi adalah 90,5%, 82,5%, 73,1%, 94,3%, 5,1, 0,1, dan 85,2%. Sensitivitas, spesifisitas, NDP, NDN, RKP, RKN, dan akurasi skoring RMI adalah 66,7%, 70%, 53,8%, 80%, 2,2, 0,4, dan 70%.*

Kesimpulan : *Metode skoring RMI modifikasi lebih akurat dalam memprediksi keganasan tumor ovarium tipe epitel dibandingkan RMI.*

Kata kunci : *CA125, keganasan, massa pelvik, RMI, tumor ovarium.*

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INTRODUCTION

Ovarian cancer is the third most cancer in women in Indonesia, which is 4.27 cases per 100000 women.[1]As the second most common gynaecological cancer in the world, most are epithelial types.[2]The absence of screening methods causes ovarian cancer is often diagnosed when the patient has a complaint or is already at an advanced stage. This brings difficulties and complexity in managing, which leads to a worse prognosis.[3]Management efficiency in patients with ovarian cancer can be improved by standardizing preoperative evaluations.

Many women with advanced ovarian cancer undergo primary suboptimal surgery in regional hospitals. The amount of tumour tissue remaining

after primary cytoreductive surgery is one of the most important prognostic factors of ovarian cancer. The type of surgery also the experience of a doctor who performs surgery is another major factor affecting the prognosis. Therefore, proper preoperative diagnosis is very crucial and is still a challenge for gynaecologists. This temporary diagnosis is useful in referring patients who are appropriate to an oncology specialist and also useful in planning appropriate operative management. The increase in morbidity and mortality rates due to the unnecessary laparotomy performed to find early-stage ovarian cancer is a clinical dilemma.[4]

Ultrasound is a standard diagnostic test to evaluate pelvic masses. Ultrasound is not invasive, inexpensive, readily available and free of ionizing radiation. Whether ultrasound can be used to distinguish benign and malignant masses has been the subject of many studies. The principles of ultrasound include confirming the presence of a mass, differentiating ovarian mass from the mass originating from the tube or uterus, describing the internal appearance of the mass and finding other abnormal appearance. It may be possible to establish a malignancy based on ultrasound appearance, but a definite diagnosis cannot always be made. Ultrasound has a high specificity of 97.7% and a positive predictive value of only 1.5%.[5]

CA125 marker tumour has been tested for their ability to distinguish malignant and benign pelvic masses. Serum CA125 elevation often precedes clinical manifestations or ultrasound detection from residual diseases in 3-6 months. Although the single value of CA125 alone is not sufficiently specific and sensitive as initial detection, its specificity increases with periodic CA125 measurements and is combined with ultrasound.[5]

In 1990 introduced the risk of malignancy index (RMI), which is the first diagnostic model that combines demographic, sonographic and biochemical parameters to investigate patients with adnexa in mass. The RMI was first modified by Tingulstad et al in 1996 (RMI2) and the second time in 1999 (RMI3). These three versions of RMI are assessed in many prospective and retrospective clinical studies. Even made RMI 4, but the validity still needs to be confirmed in future studies. The difference between these three RMIs is in the difference in USG finding scores and menopausal status. These three RMIs were tested, with evidence of criteria for malignancy on ultrasound, such as liver metastases or distant metastases and they found that RMI2 had a better performance in detecting ovarian malignancies. The value of RMI 200 has proven to be the best limit for distinguishing benign and malignant adnexal masses, with a high degree of sensitivity and specificity (51% -90% and 51% -97%).[6]

The International Ovarian Tumor Analysis (IOTA) group in 2008 had a similar system, the USG Simple Rules (SR). SR classified the tumour into benign, malignant and indeterminate. SR sensitivity 92%, and specificity 96%.[7]

IOTA SR is not an ovarian cancer screening method but is the best predictor test in the preoperative classification of an adnexal tumour. IOTA SR is simple, easy to apply, and has been validated in many reports and should be widely used in everyday medical practice.[8]

One of the goals of IOTA is to establish a method for predicting ovarian malignancy that can make ultrasound examiners who are less experienced resemble USG results performed by an experienced expert. The IOTA method has shown a better performance than RMI if an ultrasound examination is performed by a person who is less experienced. Recent evidence was conducted on 124 women, where SR had a good performance test even though it was performed by a less experienced examiner. If these results persist, then an ultrasound-based prediction method such as SR can offer a better performance test compared to biomarkers such as CA 125 and HE4 to classify ovarian abnormalities, especially when performed on premenopausal women.[8]

SR has been well received by clinicians, and the Royal College of Obstetricians and Gynecologists (RCOG) have included SR in their top green guidelines for assessing and managing ovarian mass in premenopausal patients.[9]

Researchers predict that by including the IOTA scoring system into RMI, the specificity and sensitivity of RMI can be significantly improved. It is against this background that the author wants to investigate the accuracy of RMI that has been

modified by including IOTA SR in predicting the malignancy of epithelial type ovarian tumours.

METHODS

This study was comparative research with cross-sectionalstudy design, which compares RMI modification and RMI method to predict malignancy of epithelial type ovarium tumour.

The study was conducted from October 2017 until the number of samples was met at Obstetric and Gynecology Division of RSUP Dr. M. Djamil and Laboratory of RSUP Dr. M Djamil in Padang.

The population of this study were patients with a diagnosis of ovarian tumour which would be planned for surgery at RSUP Dr. M. Djamil with the inclusion criteria had never been diagnosed with ovarian cancer before and was willing to be a research sample. Sampling technique was consecutive sampling. Each sample will be explained about information for consent and sign an informed consent.

Chi-square test was used to determine specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and accuracy with 99% CI (p≤0,01). Data were analyzed by a computer program.

RESULTS

Table 1. Characteristics of Research Subject

Characteristic	Pathological Anatomy		*P-value*
	Malign (%)	Benign (%)	
Menopausal Status			0.1
Yes	10 (50)	10 (50)	
No	11 (26.8)	30 (73.2)	
Ultrasound score			0.9
3	12 (36.4)	21 (63.6)	
1	9 (32.1)	19 (67.9)	
IOTA			0.0001
3	21 (100)	0 (0)	
1	0 (0)	40 (100)	
CA125 level			0.0001
≥ 35	20 (54.1)	17 (45.9)	
< 35	1 (4.2)	23 (95.8)	

Based on Table 1 it is known that menopausal status and ultrasound score were not associated with ovarian cystic mass (p>0,01), whereas IOTA and CA125 level had a significant relationship with ovarian cystic mass (p<0,01).

Table 2. Table 2 x 2 RMI Modifikasi

RMI Modifikasi	Pathological Anatomy		Total
	Malign	Benign	
≥ 200	19	7	26
< 200	2	33	35
Total	21	40	61

Sensitivity = a/(a+c) x 100% = 19/21 x 100% = 90.5%
Specificity PPV = d/(b+d) x 100% = 33/40 x 100% = 82.5%
NPV = a/(a+b) x 100% = 19/26 x 100% = 73.1%
PLR = d/(c+d) x 100% = 33/35 x 100% = 94.3%
NLR = {a/(a+c) : b/(b+d)} = 0,9/0,175 = 5.1
Accuracy = {c/(a+c) : d/(b+d)} = 0,1/0,8 = 0.1
= a+d / (a+b+c+d) x 100% = 52/61 x 100% = 85.2%

Sensitivity, specificity, PPV, NPV, PLR, NLR, and accuracy of RMI modification are 90.5%, 82.5%, 73.1%, 94.3%, 5.1, 0.1, and 85.2%, respectively.

Table 3. Table 2 x 2 RMI

RMI Modifikasi	Pathological Anatomy		Total
	Malign	Benign	
≥ 200	14	12	26
< 200	7	28	35
Total	21	40	61

Sensitivity = a/(a+c) x 100% = 14/21 x 100% = 66.7%
Specificity PPV = d/(b+d) x 100% = 28/40 x 100% = 70%
NPV = a/(a+b) x 100% = 14/26 x 100% = 53.8%
PLR = d/(c+d) x 100% = 28/35 x 100% = 80%
NLR = {a/(a+c) : b/(b+d)} = 0,67/0,3 = 2.2
Accuracy = {c/(a+c) : d/(b+d)} = 0,3/0,7 = 0.4
= a+d / (a+b+c+d) x 100% = 42/61 x 100% = 70%

Sensitivity, specificity, PPV, NPV, PLR, NLR, and accuracy of RMI are 66.7%, 70%, 53.8%, 80%, 2.2, 0.4, and 70%, respectively.

To find out more accurate scoring method, an analysis was carried out comparing the accuracy of RMI modification and RMI to predict the malignancy of epithelial type ovarian tumour with the following result:

Table 4. Comparison of RMI Modification and RMI Diagnostic Values

Scoring method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR	Accuracy (%)	Chi-square (p) Kappa (R)
RMI	66.7	70	53.8	80	2.2	0.4	70	0.01
RMI modification	90.5	82.5	73.1	94.3	5.1	0.1	85.2	0.35 0.0001 0.69

There was a significant relationship between ovarian tumour with RMI modification and RMI ($p \leq 0,01$) (Table 4). The result of the suitability analysis showed that the kappa values was 0.69 in the modified RMI and 0.35 in the RMI.

DISCUSSION

Based on the results of the study, it was found that Ca125 levels and ultrasound examination with the SR IOTA approach were associated with ovarian malignancy, while menopausal status and ultrasound examination with a pattern recognition approach did not have a significant relationship with ovarian malignancy. The results of Akturk et al (2011) found that Ca125 levels, menopausal status, and ultrasound examination with a pattern recognition approach had a significant association with ovarian tumour malignancy ($p < 0.001$).[10] Likewise with research conducted where there was a relationship between menopausal status, ultrasound examination with pattern recognition approach, and serum Ca125 with ovarian tumour malignancy ($p = 0.0001$.[11, 12]

In this study, a new scoring modified the RMI by replacing the ultrasound examination approach from the pattern recognition approach with the SR IOTA. The results of the analysis showed that the sensitivity of the modified RMI diagnostic test was higher at 90.5% while the RMI was 66.7%. This means that 90.5% of patients with malignant ovarian tumours will be detected with modified RMI scoring while in RMI scoring 66.7% of patients. Modification of RMI specificity was also obtained higher at 82.5% and RMI 70%. This shows that 82.5% of patients with benign ovarian tumours will give negative diagnostic tests on modified RMI scoring while RMI 70% of patients.

Modified RMI scoring method shows PPV and NPV are 73.1% and 94.3% which means that the probability of a person suffering from malignant ovarian tumours is 73.1% and the probability of someone not suffering from malignant ovarian tumours is 94.3%. PPV and NPV values using the modified RMI scoring method are higher than RMI.

The accuracy of the modified RMI scoring method is higher than the RMI of 85.2%. This means that the modified RMI diagnostic test provides more accurate results compared to the RMI method. The results showed that sensitivity, specificity, PPV, NPV, PLR, and modified RMI accuracy were higher than RMI. Statistical tests showed both scorings could be used in predicting ovarian tumour malignancy ($p \leq 0.01$), and kappa values on RMI and RMI modification were 0.35 and 0.69 which means modified RMI was better than RMI in predicting ovarian tumour malignancy.

In addition, several studies regarding RMI scoring have been carried out. All research that has been done shows that RMI can be used to predict ovarian malignancy before surgery with a value of $p < 0.01$ with various sensitivity values, specificity, PPV, NPV, PLR, NLR, and accuracy.

According to some previous studies, the IOTA SR has high sensitivity and specificity. Timmerman's research was delivered in 2010 with a sensitivity and specificity of 92% and 96%.[13]Likewise in a study with a sensitivity and specificity of 87% and 98% and which conducted an external study of one flashlight validation on 122 ovarian tumors within 4 years with the results of sensitivity and specificity of 73% and 97%. However, they did not evaluate the strategy if the IOTA SR found inconclusive results.[14]Ideally, patients with inconclusive IOTA SR results should be referred to a gynaecological ultrasound expert for further assessment[15].However, for ultrasound examiners who find it inconclusive at IOTA SR should classify it into malignancy if there is no gynaecological ultrasound expert. According to Bernardin if there is no experienced ultrasound examiner available, another alternative is to do MRI in patients.[16]However, further research is

needed for this protocol.

Another study, published in the year, was conducted on 2403 samples by comparing ADNEX models with CA125 and without CA 125, IOTA SR and RMI. Produces similar specificity of 80%, but with different levels of sensitivity, namely for ADNEX and SR IOTA between 92.3 - 93.0% compared to only 81.7% of RMI. This shows that the ADNEX and IOTA SR models have a better ability to predict malignancy than RMI.[17]In this study, it was found that the modified RMI scoring by replacing the pattern recognition ultrasound variable with IOTA SR ultrasound can be used in predicting ovarian malignancy with a p-value <0.01. If the modified RMI is compared to RMI, it is seen that the RMI modification is better than RMI. So that modified RMI can be used as a new score for predicting ovarian malignancy before surgery.

CONCLUSION

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and accuracy of RMI modification scoring are 90.5%, 82.5%, 73.1%, 94.3%, 5.1, 0.1, and 85.2%, respectively. Sensitivity, specificity, PPV, NPV, PLR, NLR, and accuracy of RMI scoring are 66.7%, 70%, 53.8%, 80%, 2.2, 0.4, 0.7, and 70%, respectively. RMI modification scoring method are more accurate to predict malignancy of epithelial type ovarian tumour than RMI.

We recommend that the pattern recognition ultrasound examination for comparison be done by the same and qualified people. For further research, it is expected that the inclusive value in IOTA will be included in malignancy to increase the sensitivity value.

REFERENCES

1. Wahidin M, Noviani R, Hermawan S, Andriani V, Ardian A, Djarir H. Population-based cancer registration in Indonesia. Asian Pac J Cancer Prev. 2012;13(4):1709-10.
2. Boyle P, Levin B. World Cancer Report 2008. World Cancer Report 2008. Geneva:Int Agency Research Cancer. 2008; 424-36.
3. Winarto H. Modification of Cutoff Values for HE4, CA125, the Risk of Malignancy Index, and the Risk of Malignancy Algorithm for Ovarian Cancer Detection in Jakarta, Indonesia. Asian Pac J Cancer Prev. 2014;15(5):1949-53.
4. Mohammed ABF, Ahuga VK, Taha M. Validation of the Risk of Malignancy Index in primary evaluation of ovarian masses. Middle East Fertil Soc J. 2014;19(4):324-8.
5. Munir SS, Sultana M, Amin D. The Evaluation of Pelvic Mass. Biomedica. 2010;26:70-5.
6. Terzic M, Dotlic J, Ladjevic IL, Atanackovic J, Ladjevic N. Evaluation of the risk malignancy index diagnostic value in patients with adnexal masses. Tai J Obstet Gynecol. 2011;68(7):589-93.
7. Abramowicz JS, Timmerman D. Ovarian mass-differentiating benign from malignant: the value of the International Ovarian Tumor Analysis ultrasound rules. Am J Obstet Gynecol. 2017;217(6):652-60.
8. Kaijser J, Bourne T, Valentine L, Sayasneh A, Holsbeke CV, Vergote I, et al. Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. Ultrasound Obstet Gynecol. 2013;41(1):9-20.
9. Timmerman D, Calster BV, Testa A, Savelli L, Fischerova D, Froyman W, et al. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. AJOG. 2016;214(4):424-37.
10. Akturk E, Karaca RE, Alanbay I, Dede M, Karasahin E, Yenen MC, et al. Comparison of four malignancy risk indices in the detection of malignant ovarian masses. J Gynecol Oncol. 2011;22:177-82.
11. Moolthiya W, Yuenyao P. The Risk of Malignancy Index (RMI) in Diagnosis of Ovarian Malignancy. Asian Pac J Cancer. 2009;10(5):865-8.
12. Ashrafganggooei T, Rezaeezadeh M. Risk of malignancy index in preoperative evaluation of pelvic masses. Asian Pac J Cancer 2011;12(7):1727-30.
13. Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839.
14. Fathallah K, Huchon C, Bats AS. External validation of simple ultrasound rules of Timmerman on 122 ovarian tumours. Gynecol Obstet Fertil. 2011;39:477-81.
15. Sayasneh A, Wynants L, Preisler J, Kaijser J, Johnson S, Stalder C, et al. Multicentre external validation of IOTA prediction models and RMI by operators with varied training. Bri J Cancer. 2013;108:2448-54.
16. Bernardin L, Dilks P, Liyanage S, Miquel ME, Sahdev A, Rockall A. Effectiveness of semi-quantitative multiphase dynamic contrast-enhanced MRI as a predictor of malignancy in complex adnexal masses: radiological and pathological correlation. Eur Radiol. 2012;22(4):880-90.
17. Froyman W. Performance of the RMI and IOTA ADNEX and Simple Rules risk model in the evaluation of adnexal masses not classifiable using the Easy Descriptors as first step. Ultrasound Obstet Gynecol. 2017;50(S1).

Research Article

Characteristics, Management and Survival Rate of Ovarian Germ Cell Tumor

Karakteristik, Manajmen, dan Tingkat Kesintasan Ovarian Germ Cell Tumor

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Abstract

Objective : To determine the prevalence of malignant ovarian germ cell tumour in term of characteristics, management, and 3-year survival rate in Dr. Cipto Mangunkusumo Hospital Jakarta from 2011 to 2013.

Methods : This is a cross-sectional study. Secondary data were collected from medical record as well as interviewing patients through phone call or home visit.

Results : We collected data from 24 subjects. As many as 54.2% of subjects were between 20 to 40 year old, and 58.3% was single. Around 83.3% of the subjects came with chief complaint of abdominal enlargement. Histopathology finding confirmed dysgerminoma in 50% subjects, mixed ovarian germ cell tumour in 25%, endodermal sinus tumour or yolk sac tumour in 16.7%, and immature teratoma in 8.3%. Half of the cases were found in stage I. The primary therapy was conservative surgical staging and adjuvant chemotherapy.In 2 subjects with dysgerminoma, neoadjuvant chemotherapy (bleomycin, etoposide, cisplatin, and cyclophosphamide-cisplatin regimen) resulted in a good response. The 3-year survival rate was 83.3% in dysgerminoma, 100% in mixed ovarian germ cell tumour, and 50% in immature teratoma.

Conclusions : In malignant ovarian germ cell tumour, conservative surgical staging followed by a complete course of chemotherapy is the treatment of choice with 3-year survival rate exceeding 70%.

Keywords : dysgerminoma, non-epithelial ovarian tumour,ovarian germ cell tumour, survival.

Abstrak

Tujuan : *Mengetahui sebaran meliputi karateristik, penatalaksanaan dan kesintasan 3 tahun pasien tumor ganas sel germinal ovarium di RSCM tahun 2011 – 2013.*

Metode : *Penelitian ini menggunakan studi potong lintang dengan mengambil data sekunder dari rekam medis dan mewawancarai pasien atau keluarga pasien via telepon atau kunjugan rumah.*

Hasil : *Pada penelitian ini, dari 24 subjek penelitian, 54,2% ditemukan pada usia 20-40 tahun dan 58,3% subjek belum menikah. Sebanyak 83,3% datang dengan keluhan perut membesar. Secara histopatologi didapatkan jenis disgeminoma, tumor sel germinal campuran, sinus endodermal (yolk sac) dan teratoma imatur dengan proporsi masing-masing 50%, 25%, 16,7% dan 8,3%, sebagian besar kasus (50%) ditemukan pada stadium I. Conservative surgical staging dan kemoterapi adjuvan tatalaksana pilihan. Terdapat 2 subjek jenis disgerminoma yang diberikan dengan kemoterapi neoadjuvan (regimenbleomycin, etoposide, cisplatin dan cyclophosmide-cisplatin) memberikan respon yang baik. Kesintasan ≥ 3 tahun pada jenis disgerminoma mencapai 83,3%, pada tumor sel germinal campuran 100% dan pada teratoma imatur mencapai 50%.*

Kesimpulan : *Pada tumor ganas sel germinal ovarium conservative surgical staging diikuti kemoterapi lengkap merupakan pilihan terapi dengan kesintasan ≥ 3 tahun mencapai > 70%.*

Kata kunci : *disgerminoma,kesintasan, tumor ovarium non epithelial, tumor sel germinal ovarium.*

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INTRODUCTION

Around 70% of ovarian tumour that affects teenager and young adult is ovarian germ cell tumour and one-third of the total cases is malignant.[1]Malignant ovarian germ cell tumour is a rare occurrence, accounts for 5% of total ovarian malignancy.[2]Unlike malignant neoplasm from epithelial ovary cells, this type of tumour affects women in reproductive age, including teenager and young adult.

According to *Surveillance, Epidemiology and Results* (SEER) in 1973 to 2003, identification in 1,262 patients with malignant ovarian germ cell tumour showed dysgerminoma in 32.4% cases, immature teratoma with malignant degeneration in 35.6% cases, and mixed germ cell tumour in 28.7% cases.[3]In Asian and African population, the most common type of malignant ovarian germ cell tumour is dysgerminoma.[4]

Management in malignant ovarian germ cell tumour has improved dramatically, giving rise to improvement in survival rate. Survival rate reaches 100% in dysgerminoma type and 85% in non-dysgerminoma type.[5] Treatment in ovarian germ cell tumour used to result in impaired fertility.[6]In the 1980s, reserving fertility could only be performed in stage 1 and 2 malignant ovarian germ cell tumour with normal contralateral ovary and uterus. Starting in 1989, fertility function could be well maintained in all stage of the tumour, even in patients with involvement of both ovaries.[7]

Compared to data on testicle germ cell tumour, data in Indonesia regarding ovarian germ cell tumour is scarce. Therefore, we collected and analyzed the data to determine the prevalence and management of malignant ovarian germ cell in Indonesia, especially in Jakarta.

METHODS

This is a cross-sectional study. Secondary data were collected from the medical record and from interviewing patients. The interview was performed via phone call or home visit to determine the 3-year survival rate. We recruited all patients with malignant ovarian germ cell tumour who received a complete course of therapy in Dr. Cipto Mangunkusumo Hospital Jakarta from 2011 to 2013.

We calculated the sample size based on prior data on disease prevalence in Asia. The result was 49 subjects. Subjects were recruited with total sampling from cancer registration in the oncology division of Obstetrics and Gynecology Department. Collected data were analyzed with the Statistical Program for Social Sciences (SPSS) 20. Ethical clearance was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia, in August 2017.

RESULTS

There were 57 patients with malignant ovarian germ cell tumour in Cipto Mangunkusumo Hospital Jakarta from 2011 to 2013. However, only 24 subjects fulfilled the inclusion criteria of having a complete medical record. Baseline characteristics of the subjects are presented in table 1.

Table 1. Subjects Baseline Characteristics and Histopathology Finding

Variables (n : 24)	n	%
Age (yo)		
10-19	1	1
20-40	13	13
≥ 40	10	10
Marital status		
Single	14	14
Married	10	10
Parity		
0	14	14
≤ 2	7	7
> 2	3	3
Chief complaint		
Abdominal enlargement	20	20
Abdominal pain	4	4
Ultrasound/chest X-ray		
No ascites and effusion	12	12
Ascites or effusion	9	9
Ascites and effusion	3	3
Histopathology		
Dysgerminoma	12	12
Mixed germ cell tumour	6	6
Endodermal sinus tumour (yolk sac)	4	4
Immature teratoma	2	2

We also collected data on tumour marker examination. Most of the subjects with dysgerminoma had raised the level of lactate dehydrogenase (LDH). We found two (16.7%) subjects with cancer antigen 125 (CA125) elevation, which is uncommon as Ca125 elevation is usually associated with the ovarian epithelial tumour. In three (25%) subjects, elevation in LDH was accompanied with other tumour marker elevation such as alpha-fetoprotein (AFP), human Chorionic Gonadotrophin (bHCG) and CA125. Another significant elevation of a tumour marker is presented in Table 2.

Table 2. Tumor Marker Findings

Variables	n	%
Dysgerminoma (n : 12)		
Elevated LDH	6	50
Elevated Ca125	2	16.7
Elevated bHCG	1	8.3
Elevated LDH, Ca125	2	16.7
Elevated LDH, AFP, bHCG	1	8.3
Mixed germ cell tumor		
Elevated LDH	3	50
Elevated Ca125	3	50
Endodermal sinus tumor		
Elevated AFP	2	50
Elevated AFP, Ca125	1	25
Elevated AFP, LDH, Ca125	1	25
Immature teratoma (n : 2)		
Elevated LDH	2	100

Table 3. Clinical Staging Grouped by Histopathology Type.

Variables	n	%
Dysgeminoma (n : 12)		
Stage 1	8	66.7
Stage 3	2	16.7
Stage 4	2	16.7
Mixed germ cell tumor (n : 6)		
Stage 1	4	66.7
Stage 3	2	33.3
Endodermal sinus tumor (n : 4)		
Stage 1	2	50
Stage 2	2	50
Immature teratoma (n : 2)		
Stage 1	1	50
Stage 3	1	50

Furthermore, we noted clinical staging from each subject grouped by type of histopathology findings, as shown in Table 3.

In term of case management, unilateral salphingo-oophorectomy (USO) was performed in half of the total subjects with or without omentectomy, appendectomy, and lymphadenectomy.

Options for chemotherapy were grouped based on histopathology type of the tumour. Half of the subjects with dysgerminoma underwent complete series of cisplatin, vinblastine, and bleomycin (PVB); bleomycin, etoposide, and cisplatin (BEP); and cyclophosphamide-cisplatin (CP) with the proportion of 8.3%, 25%, and 16.7% consecutively. The rest of the subjects did not undergo chemotherapy.

In term of 3-year survival rate, most of the patients (70.8%) were alive, and 83.3% were asymptomatic.

We analyzed survival functions with Kaplan Meier curve and found that all patients with stage 3 and 4 tumour despite their histopathology type had a 3-year survival rate of 100% with treatment. Similarly, the 3-year survival rate for patients with neoadjuvant chemotherapy is 100%. We also found that 3-year survival rate in dysgerminoma with complete treatment is higher than endodermal sinus tumour, immature teratoma, and mixed germ cell tumour.

DISCUSSION

The highest prevalence of malignant ovarian germ cell tumour was found in age 20 to 40 year old, followed by those older than 40, and younger than 20. This finding agrees with prior epidemiological data in which the highest incidence of malignant ovarian germ cell tumour occurs in young females aged 15 to 30-year-old.[8]However, one study stated that the highest incidence is within 15 to 19 year old.3 Up until 20 years old, almost 70% of ovarian tumour originates from germ cells, and one-third of this number proves to be malignant.6 The tendency of malignancy in younger age may be caused by a hormonal factor as in the high level of exogenous and endogenous estrogen that disturbs the development of germ cell from primitive to mature cells. These abnormal germ cells are retained until puberty in which gonadotropin further initiates proliferation and results in tumour with various histopathology.[9]

In this study, most of the patients came with a chief complaint of abdominal enlargement. This is inconsistent with several other studies that presented abdominal pain and distention as their chief complaints.[10,11]

We found that most of our subjects had dysgerminoma. This is consistent with epidemiology data from that stated dysgerminoma as the most frequent type of malignant ovarian germ cell tumour.[10]Another important finding we need to highlight is tumour marker test. Carcinoembryonic antigen (CEA) is associated with gastrointestinal tract tumour. However, 4 of our subjects underwent this test that we think is unnecessary. Elevation in CA125 may be caused by various factors since this tumour marker is usually associated with ovary epithelial cell tumour. Each of our subjects underwent a test for multiple types of tumour markers, and therefore, we found overlapping results. However, we only presented results with significant elevation.

Study on tumour marker found that there were 7 significant tumour markers associated with various type of germ cell tumour in ovary. CA125 was found in more than 50% of the subjects. AFP was found positive mostly in endodermal sinus tumour (100%), immature teratoma (61.9%), and dysgerminoma (11.8%). Significant elevation of LDH was found in 95% of dysgerminoma cases and 83.3% of endodermal sinus tumour. CEA is considered not associated with germ cell ovary tumor.[12]

Half of our subjects did not present with ascites or effusion. This condition may be caused by the fact that ascites or peritonitis due to effusion is a secondary manifestation from torsion, infection, or ovarian tumour rupture.[13]

Unilateral Salphingo-Oophorectomy (USO) was performed in 50% subjects in which 5 of them underwent additional procedures (omentectomy, appendectomy, and / or lymphadenectomy) due to the younger age and marital status of most subjects. One subject underwent bilateral salphingo-oophorectomy (BSO), and 11 subjects underwent total hysterectomy with BSO. In a study by Weinberg et al in 2011, USO was performed in 67.5% patients while total hysterectomy with BSO in 25% of patients. This study only examined subjects with surgery and preserved fertility.[5]

In term of histopathology, dysgerminoma, mixed germ cell tumour, endodermal sinus tumour, and immature teratoma, more than 50% were found in stage I. This finding agrees with epidemiology data which stated that 60-70% cases were FIGO stage I or II.[11]

Malignant ovarian germ cell tumour is sensitive to chemotherapy. The standard regimen for non-dysgerminoma cases is BEP.[14] In a study, 75% of patients with adjuvant chemotherapy postoperatively, 77% received BEP regimen. One patient with immature teratoma stage IIIc grade 2-3 was given additional VAC regimen when the tumour recurred.[5] In our study, only 10 subjects completed 6 series of chemotherapy, 8 of them had adjuvant chemotherapy (6 with PEB regimen, 1 with PVB regimen, and 1 with CP regimen) while the remaining 2 had neoadjuvant chemotherapy with BEP and CP regimen. Both groups presented a satisfying result.

We did not find any VAC regimen in our data. There are no recurrent cases, and therefore we never used VAC regimen. Three patients with dysgerminoma had total abdominal radiotherapy, and 10 patients (5 with dysgerminoma and 5 with immature teratoma) did not receive postoperative adjuvant therapy unless 1 patient with stage Ia dysgerminoma with recurrence.5 In our study, we did not examine radiotherapy treatment, and we did adjuvant chemotherapy for dysgerminoma, mixed germ cell tumour, endodermal sinus tumour, and immature teratoma patients although chemotherapy was only performed in 42% subjects.

Overall survival rate was 100%. Based on epidemiology data, the majority of patients with ovarian germ cell malignancy has high cured rate with a small proportion experiencing recurrence within 24 months after primary diagnosis.[14]As many as 71% of our subjects survived for at least 3 years after surgery. Based on histopathology type, dysgerminoma, mixed germ cell tumour, and immature teratoma had a 3-year survival rate of 83.3%, 100%, and 50% consecutively. Endodermal sinus tumour cases had a less-than-3-year survival rate of 100%.

We had 7 subjects who had survival duration of less than 3 years. This event may be caused by a certain tendency to refuse chemotherapy. We did not examine the recurrence or progression of the disease.

This study examined rarely evaluated epidemiology data. There is no recent data on

characteristic, management, and survival rate of patients with malignant germ cell tumour of the ovary, especially in Dr. Cipto Mangunkusumo Hospital Jakarta. Furthermore, there is no standard management guideline for such cases. However, we are also aware of a weakness in this study. In particular, we had inadequate subjects. The sample size was calculated with a minimal of 49 subjects. We only managed to recruit 24 subjects due to incomplete medical record data. We were unable to contact patients to learn about their current condition. Patients who live out of town presented as a challenge because we cannot perform the necessary physical and supporting examination to detect recurrence. Without routine follow-up, we lost contact from most of our patients.

CONCLUSION

Malignant ovarian germ cell tumour occurs mostly in teenagers, and young adult (20 to 40-year-old) and the most common type is dysgerminoma. Tumour marker elevation may differ based on histopathology. In dysgerminoma, mixed germ cell tumour, and immature teratoma, we found elevation in LDH while elevated AFP was found in endodermal sinus tumour.

All type of malignant ovarian germ cell tumour is mostly detected in stage I. Unilateral salphingo-oophorectomy (conservative surgical staging) followed with adjuvant chemotherapy (BEP regimen) is still the treatment of choice, especially for nulliparous patients. With adequate treatment (surgery and chemotherapy), patients with malignant ovarian germ cell tumour had 71% 3-year survival rate.

REFERENCES

1. Zalel Y, Piura B, Elchalal U, et al. Diagnosis and management of malignant germ cell ovarian tumours in young females. Int J Gynecol Obstet 1996; 55:1.
2. Quirk JT, Natarajan N, Mettlin CJ. Age-Specific Ovarian cancer Incidence Rate Patterns in The United States. Gynecol Oncol. 2005;99(1):248–50.
3. Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, et al. Incidence and survival rates for female malignant germ cell tumours. Obstet Gynecol. 2006;107(5):1075–85.
4. Pectasides D, Pectasides E, Kassanos D. Germ cell tumours of the ovary. Cancer Treat Rev. 2008 ;34(5):427–41.
5. Weinberg LE, Lurain JR, Singh DK, Schink JC. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumours. Gynecol Oncol. 2011;121(2):285–9.
6. Low JJH, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynecol. 2012 ;26(3):347–55.
7. Lai C-H, Chang T-C, Hsueh S, Wu T-I, Chao A, Chou H-H, et al. Outcome and prognostic factors in ovarian germ cell malignancies. Gynecol Oncol. 2005 ;96(3):784–91.
8. DiSaia P, Creasman W. Epithelial ovarian cancer. Clinical Gynecologic Oncology, 6th ed. Mosby: 2002; 9:289-350.
9. Walker AH, Ross RK, Haile RW, Henderson BE. Hormonal factors and risk of ovarian germ cell cancer in young women. Bri J Cancer 1988;57:418-22.
10. Koshy M, Vijayananthan A, Vadiveloo V. Malignant ovarian mixed germ cell tumour: a rare combination. Biomed Imaging Interv J 2005;1(2). Available from: http://www.biij.org/2005/2/e10
11. Gershenson DM. Management of Ovarian Germ Cell Tumors. J Clin Oncol. 2007 ;25(20):2938–43.
12. Kawai M, Kano T, Kikkawa F, Morikawa Y, Oguchi H, Nakashima N, et al. Seven tumor markers in benign and malignant germ cell tumors of the ovary. Gynecol Oncol 1992;45:248-53.
13. Tewari K, Cappuccini F, Disaia PJ, Berman ML, Manetta A, Kohler MF. Malignant germ cell tumors of the ovary. Obstet Gynecol 2000;95(1):128–33
14. Williams SD, Blessing JA, DiSaia PJ, et al. Second-look laparotomy in ovarian germ cell tumors: The Gynecologic Oncology Group experience. Gynecol Oncol. 1994;52:287-91.

Case Report

Old Perineal Rupture: From Diagnosis to Reparation

Ruptur Perineum Lama: Diagnosis sampai Perbaikan

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Abstract

Objective : To describe and discuss the technique to diagnose, preparing the reparation and postoperative management in old perineal rupture case.

Methods : A 28-year-old primipara woman was referred to YPK Mandiri Hospital after having incontinence to flatus, to urinate and passive soiling. Three months before admission, she had her first child through vaginal delivery.

Discussion : She was diagnosed with a third-degree obstetric anal sphincter injury (OASIS). Rectal examination with digital palpation (pill-rolling motion) and ultrasound examination, revealed a distinct gap anteriorly (10 – 2 o'clock). End to end technique was preferred to repair the defect.

Conclusions : A good understanding of perineal and anal sphincter anatomy is essential to diagnose OASIS. The aim of reconstructive surgery is to restore the continuity of both the external and internal anal sphincters. Ideally, the repair should be performed as soon as possible after the injury.

Keywords : obstetric anal sphincter injuries, OASIS, third-degree tear, perineum, perineal trauma.

Abstrak

Tujuan : *Untuk mendeskripsikan dan diskusi tentang tehnik dalam mendiagnosa, mempersiapkan operasi reparasi dan manajemen pascaoperasi pada kasus ruptur perineum lama.*

Metode : *Sebuah laporan kasus yang diambil dari pasien perempuan 28 tahun primipara yang dirujuk ke RS YPK Mandiri setelah mengeluhkan inkontinensia flatus, urin, dan keluarnya feses tanpa disadari. Tiga bulan sebelumnya, pasien melahirkan anak pertama melalui persalinan pervaginam.*

Diskusi : *Diagnosis pasien adalah cedera sfingter ani obstetrik derajat tiga. Pemeriksaan rektal dengan palpasi digital (gerakan pill-rolling) dan pemeriksaan ultrasonografi, memperlihatkan adanya penipisan di daerah anterior (arah jam 10 – 2). Teknik end to end dipilih untuk memperbaiki defek.*

Kesimpulan : *Pengetahuan yang baik mengenai anatomi perineum dan sfingter ani penting untuk mendiagnosis OASIS. Tujuan utama dari operasi rekonstruksi adalah untuk memperbaiki kontinuitas dari sfingter ani eksternal dan internal. Idealnya, reparasi dilakukan secepat mungkin setelah terjadinya cedera.*

Kata kunci : *cedera sfingter ani obstetrik, OASIS, perineum, trauma perineum, robekan derajat tiga.*

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INTRODUCTION

OASIS includes both third- and fourth-degree perineal tears. Third-degree perineal tears are defined as partial or complete disruption of the anal sphincter muscles, which may involve either or both the external anal sphincter (EAS) and internal anal sphincter (IAS) muscles.[1]In developed countries, the incidence of third-degree perineal tears ranges between 0.5% and 1% of all vaginal deliveries and are significantly more common in primigravidae.[2]The rareness and difficulty in identifying the torn parts of the perineal muscles make it difficult to be diagnosed, and there are still difference perspectives in the repair techniques.

Case Illustration

A 28-year-old primipara woman was referred to our centre (YPK Mandiri Hospital). Three months prior to referral to our centre, she had her first child through vaginal delivery by a midwife. A month later, she having anal incontinence,

urinary incontinence, and bowel contents could leak passively. Her gynaecologist diagnosed her with an obstetric anal sphincter injury (OASIS), and she got referred.

Through inspection, the perineal body was absent, and there was an absence of the corrugator cutis anal. We did rectal examination and pill rolling motion and found a thinning anteriorly. On transperinealultrasound examination, we found a distinct gap and discontinuation at 10 – 2 o'clock (Figure 1).

Figure 1. Ultrasound imaging

We diagnosed her with an old third-degree perineal rupture (grade 3C). We recommended a surgical repair of third-degree tear. The procedure was done using regional anaesthesia. We got a complete and retracted rupture of the internal anal sphincter muscles and external anal sphincter muscles. The IAS muscle was repaired separately with interrupted sutures using 3/0 polyglactin suture on a tapered needle. The repair of EAS muscle used end to end technique and its capsule using interrupted sutures; using 2/0 polyglactin suture on a tapered cut needle. Then we rebuild the distal rectovaginal septum and perineal body using 2/0 polyglactin suture on a cutting needle. We reconstruct the perineal body to provide support to the repaired anal sphincter. Then the vaginal skin was sutured and the perineal skin approximated with a Vicryl 3/0 subcuticular suture. A rectovaginal examination was performed to confirm complete repair and ensure that all tampons or swabs have been removed.

DISCUSSION

Obstetric damage to the anal sphincter includes both third and fourth-degree perineal tears.[1] Third-degree perineal tears are defined as partial or complete disruption of the anal sphincter muscles, which may involve either or both the external anal sphincter (EAS) and internal anal sphincter (IAS) muscles.[1,3-5]

The diagnostic examination used in our case was transperineal ultrasound imaging. The transperineal approach using a high frequency transvaginal probe for evaluation of the anatomy of the anal sphincter has been presented by several investigators[6,7] as it is more accessible to obstetricians that seem to be well tolerated.[8]Other studies recommend using endoanal ultrasonography and magnetic resonance imaging.[9]The vaginal probe was placed in the area of the fourchette and perineal body, and the area was scanned in the transverse and sagittal planes. The internal sphincter appears as a hypoechoic ring. The external sphincter appears as a double ring of mixed echogenicity with a thin hypoechogenic layer between two layers of mixed echogenicity. When defects were suspected, they were evaluated for irregularity and discontinuity of the normaland hyperechoic rings. Discontinuity of the sphincter, changes in sphincter width or asymmetry, the 'half-moon' sign, and changes in the pattern of mucosal folds the 'star sign' are potentially useful sonographic features of sphincter muscle damage.[8]

The aim of reconstructive surgery (either primary or secondary) is to restore the continuity of both the external and internal anal sphincters. Proper reconstruction will also result in the lengthening of the anal canal and restoration of a functional high-pressure zone within it.[7] The goal of sphincter repair is reconstructing a muscular cylinder that is at least 2 cm thick and 3 cm long,[10,11] as this results in an anatomically and functionally correct anal canal. Meticulous hemostasis and anatomic reapproximation of all disrupted tissue layers are the key principles for preventing complications and restoring faecal competence.[5]

Adequate anesthesia is required to relax the contracted anal sphincter, retrieve the retracted ends, and bring them back together without tension.[1,5,12]Anesthesia should always be used, and epidural anesthesia is considered to be the gold standard type.[2]

For the choice of sutures for repair, one of personal preference. In general, rapidly absorbed

suture material is not appropriate for third and fourth-degree tears.[1] Chromic catgut has been largely replaced by synthetic, delayed absorbable materials, such as polyglactin 910 and polyglycolic acid, as these materials are associated with less pain, less need for analgesia and less resuturing for dehiscence.[1,13-15]Diameter of the suture should be considered; 2/0 and 3/0 sutures are suitable for soft tissue repair.[1,2,5]Monofilament sutures may cause less tissue reaction than braided sutures, thus may minimize discomfort and infection risk.

The patient was diagnosed with an old third-degree perineal rupture (grade 3C) as both EAS and IAS torn.[1,4,5,9,10]The optimal repair consists of a multilayer closure. The IAS should be repaired as a separate layer.[1,2,4,10]It often retracts laterally and superiorly and appears as thickened, pale pink, shiny tissue just above the anal mucosa. Reapproximation of this layer is important for the strength and integrity of the repair and for achieving anal continence. The repair of EAS begins by identifying and grasping the two severed ends of the dark red external anal sphincter muscle with Allis clamps, and it may be necessary to push the clamp deep into the surrounding connective tissue to locate the sphincter since one or both ends typically retract when it ruptures. The repair of the muscle consists of either an end-to-end or overlapping plication of the disrupted muscle and its capsule using interrupted or figure-of-eight sutures.[2,4,6]In this patient, we use the end-to-end technique due to the extension of the retraction, thus making us unable to overlap the muscle. Proper overlap is possible only when the full length of the torn ends of the EAS is identified. By contrast, an end-to-end technique can be performed without identifying the full length of EAS, giving rise to incomplete apposition.[4]The end-to-end technique is used to bring the ends of the sphincter together at each quadrant. (12, 3, 6, and 9 o'clock) using interrupted sutures placed through the capsule and muscle.[2]Compendiously there was no significant advantage between overlap repair and approximation technique concerning faecal incontinence at one year.[16,17]

The perineal muscles should be sutured to reconstruct the perineal body to provide support to the repaired anal sphincter. Furthermore, a short deficient perineum would make the anal sphincter more vulnerable to trauma during a subsequent vaginal delivery.[4] A continuous non-locking suturing technique to oppose each layer (vaginal tissue, perineal muscle, and skin) is associated with less short-term pain compared to traditional interrupted method.[1,2,5]It is important to do a rectovaginal examination to confirm complete repair and ensure that all tampons or swabs have been removed after finishing the procedure.[4]

For the post-repair management, A Foley catheter should be inserted for about 12-24 hours before bladder sensation returns or until the swelling subsides.[2,4]Administration of laxatives for a few days (2-10 days) is recommended in order to reduce the mechanical stress on the sutures and wound dehiscence.[2-4]Should be remembered that postoperative pain, rate of wound infections, continence, and dyspareunia are not affected by the administration of the laxatives.3The rate of wound complications after third-degree perineal tears (wound infection, dehiscence, reoperation, readmission to the hospital) amounts to 7,3%.[3]Analgesia is required to reduce the postsurgical pain. Avoid codeine containing analgesics as they may lead to constipations, leading to excessive straining and possible disruption of the repair.[1,3,4]

CONCLUSION

There is no difference in methods and postoperative managements between primary and secondary sphincter repair. A good understanding of perineal and anal sphincter anatomy is essential to diagnose OASIS. The aim of reconstructive surgery is to restore the continuity of both the external and internal anal sphincters. Ideally, the repair should be performed as soon as possible after the injury.

CONSENT

Written informed consent was obtained from the patient for the case report and any accompanying images publication.

DISCLOSURE POLICY

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. King Edward Memorial Hospital. Management of third & fourth degree perineal trauma. Clin Guide Obstet Midwifery. 2014:1-4.
2. Daniilidis A, Markis V, Menelaos T, Loufopoulos P, Hatzis P, et al. Third-degree perineal lacerations – How, why and when? A review analysis. Open Journ of Obstetrics and Gynecology, 2012(2):304-10. Available from: http://dx.doi.org/10.4236/ojog.2012.23064
3. Aigmuller T, Bader W, Beilecke K, Elenskaia K, Frudinger A, et al. Management of 3rd and 4th-degree perineal tears after vaginal birth. German Guideline of the German Society of Gynecology and Obstetrics. Geburtsh Frauenheilk, 2015; 75: 137-44.
4. Sultan, AH, Thakar R. Third and Fourth Degree Tears. In: Sultan AH, Thakar R, Fenner DE. Perineal and Anal Sphincter Trauma Diagnosis and clinical Management. Springer, 2007: 33-51.
5. Toglia MR. Repair of perineal and other lacerations associated with childbirth. Up to Date, 2017:1-25.
6. Yagel S, Valsky DV, Hamani Y. Evaluationg obstetric tears to the anal sphincter by transperineal 3D ultrasound. (abstract) ISUOG: Stockholm, Sweden, 2004.
7. Timor-Tritsch IE, Monteagudo A, Smilen SW, Porges RF, Avizova E. Simple ultrasound evaluation of the anal sphincter in female patients using a transvaginal tranducer. Ultrasoud Obstet Gynecol 2005;25:206-9.
8. Valsky DV, Messing B, Petkova R, Savchev S, Rosenak D, et al. Postpartum evaluation of the anal sphincter by transperineal three-dimensional ultrasound in primiparous women after vaginal delivery and following surgical repair of third-degree tears by the overlapping technique. Ultrasound Obstet Gynecol 2007;29:195-204. Available from: http://dx.doi.org/10.1002/uog.3923
9. Faltin DL, Boulvain M, Floris LA, Irion O. Diagnosis of anal sphincter tears to prevent fecal incontinence: a randomized controlled trial. Obstet Gynecol 2005;106:6-13.
10. Delancey JO, Toglia MR, Perucchini D. Internal and external anal sphincter anatomy as it relates to midline obstetric lacerations. Obstet Gynecol 1997;90:924.
11. Aronson MP, Lee RA, Berquist TH. Anatomy of anal sphincters and related structures in continent woman studied with magnetic resonance imaging. Obstet Gynecol 1990;76:846.
12. Sultan AH, Monga AK, Kumar D, Stanton SL. Primary repair of obstetric anal sphincter rupture using the overlap technique. Br J Obstet Gynaecol. 1999;106(4):318-23. PubMed PMID: 10426237. Available from: https//www.ncbi.nlm.nih.gov/pubmed/10426237.
13. Mackrodt C, Gordon B, Fern E, et al. The Ipswich Childbirth Study: A randomized comparison of polyglactin 910 with chromic catgut for postpartum perineal repair. Br J Obstet Gynaecol, 1998;105:441.
14. Greenberg JA, Lieberman E, Cohen AP, Ecker JL. Randomized comparison of chromic versus fast-absorbing polyglactin 910 for postpartum perineal repair. Obstet Gynecol 2004;103:1308.
15. Kettle C, Dowswell T, Ismail KM. Absorbable suture materials for primary repair of episiotomy and second-degree tears. Cochrane Database Syst Rev 2010;:CD000006.
16. Rygh, AB, et al. The overlap technique versus end-to-end approximation technique for primary repair of obstetric anal sphincter rupture: A randomized controlled study. Acta Obstetricia et Gynecologica Scandinavica, 2010;89:1256-62.
17. Royal College of Obstetricians and Gynecologists. The management of third- and fourth-degree perineal tears. Green-Top Guideline, 2015;29:1-19.