The 1st International Pharmacy Conference on Research and Practice

PROCEEDING

TOWARD EXCELLENT IN NATURAL PRODUCTS: PRESERVING TRADITIONS, EMBRACING INNOVATIONS

Supported by :

BTN Syariah

Organized by :

UNIVERSITAS ISLAM INDONESIA

DEPARTMENT OF PHARMACY
FACULTY OF MATHEMATICS AND NATURAL SCIENCE
ISLAMIC UNIVERSITY OF INDONESIA

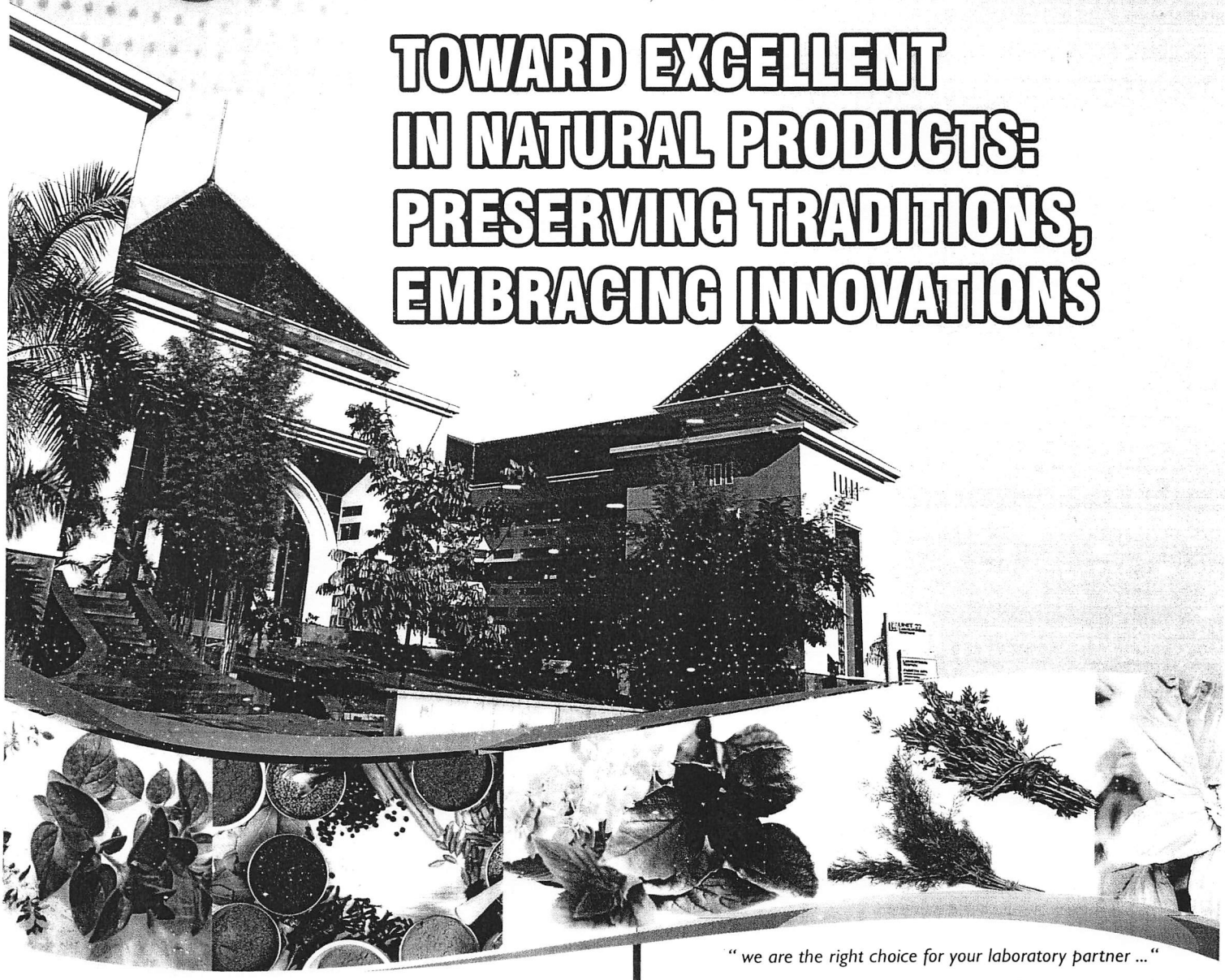
B.5 & B.6

IPCRP

The 1st International Pharmacy Conference on Research and Practice

PROCEEDING

TOWARD EXCELLENT IN NATURAL PRODUCTS: PRESERVING TRADITIONS, EMBRACING INNOVATIONS



Supported by :

BTN Syariah

Organized by :

UNIVERSITAS ISLAM INDONESIA

DEPARTMENT OF PHARMACY
FACULTY OF MATHEMATICS AND NATURAL SCIENCE
ISLAMIC UNIVERSITY OF INDONESIA

The 1st International Pharmacy Conference on Research and Practice

PROCEEDING

TOWARD EXCELLENT IN NATURAL PRODUCTS: PRESERVING TRADITIONS, EMBRACING INNOVATIONS

Supported by :

BTN

Organized by :

DEPARTMENT OF PHARMACY
FACULTY OF MATHEMATICS AND NATURAL SCIENCE
ISLAMIC UNIVERSITY OF INDONESIA

DEPARTMENT OF PHARMACY

FACULTY OF MATHEMATICS AND NATURAL SCIENCE

ISLAMIC UNIVERSITY OF INDONESIA

Kaliurang Street Km 14.5 Yogyakarta, Indonesia, 55584

Phone : +62-274-895920

Email : pharcon@uii.ac.id

Http : //pharconuii.com

ISBN 978-979-98417-4-2

9 789799 841742

First Printed – 2012

Publisher:
Department of Pharmacy
Islamic University of Indonesia, Kaliurang Street, Km 14.5 55584
Phone. (0274) 895929; 898582 ext. 3021 Fax. (0274) 896439
Email: fmipa@uii.ac.id

Republic of Indonesia National Library Cataloging-in-Publication Data

International Pharmacy Conference on Research and Practice (ke-1 : 2012 : Yogyakarta)
The 1 st International Pharmacy Conference on Research and Practice : Conference Proceeding/ editor, Hayati. -- Yogyakarta : Program Studi Farmasi FMIPA UII, 2012.
179 hlm. : 21 X 29.7cm.
ISBN 978-979-98417-4-2
1. Farmasi – Kongres. I. Judul. II. Hayati.

615.106

Preface

The 1st **International Pharmacy Conference on Research and Practice (IPCRP)** was held on 13th - 14th November 2012 at the Sheraton Hotel in Jogjakarta and organized by Department of Pharmacy, Islamic University of Indonesia. In this conference, pharmacists and other health professions from different fields have been participated. The main theme of the 1st IPCRP is ***"Toward Excellent In Natural Products: Preserving Traditions, Embracing Innovations"***, which breakdown into 3 sub-themes broadly representing herbal medicine; advance research in pharmacogenomics and proteomic; and also pharmacist's role in practice.

Therefore, in order to disseminate the results of the conference into the broader community, this proceeding is produced. This proceeding features a number of papers presented in the conference, either oral or poster presentation, which represent 4 themes: Industrial Pharmacy; Natural Product and Phytotherapy; Biomedical and Biotechnology; Clinical and Community Pharmacy.

On behalf of the organizing committee, sincere appreciation are expressed to the Ministry of Research and Technology Republic of Indonesia for his kindness to give keynote lecture in this conference, members of the Organizing Committee for the good teamwork and the great effort, and also for all sponsors for good collaboration in bringing forth the conference. We also would like to thank all participants for many fruitful discussions and exchanges that contributed to the success of the conference.

Finally, we hope that this proceeding will give beneficial contribution toward improving the scientific atmosphere, especially in the field of Pharmaceutical Sciences and Pharmacy Practices.

Yogyakarta, November 2012

Rochmy Istikharah, M.Sc., Apt
Chairperson of Organizing Committee

Contents

Natural Products and Phytotherapy

B-6

THE CONTROVERSY OF USE OF HORMONAL REPLACEMENT THERAPY (HRT) IN WOMEN POST MENOPAUSE : PRELIMINARY STUDY IN INDONESIA

Syaefudin Ali Akhmad [1], Erlina Marfianti[2], Yasmini Fitriyati[3], Endang Wahyuningsih[4]

[1]Departement of Biochemistry Islamic University of Indonesia Faculty of Medicine
[2]Departement of Internal Medicine Faculty of Medicine, Islamic University of Indonesia
[3]Departement of Obstetrics and Gynecology, Faculty of Medicine, Islamic University of Indonesia
[4]Internal Medicine Specialist Clinic of Klaten Islamic Hospital of Central Java

Correspondence :
saafkuii@gmail.com
Jl. Kaliurang Km 14,5 Kampus Terpadu FK UII Sleman Jogjakarta 0274 898444 ext 2097

Abstract

The number of postmenopausal women in the world in 2020 according to the World Health Organization is expected to reach 1.2 billion, while in Indonesia, according to the Central Beraeu of Statistic (CBS) number of postmenopausal women in 2025 will reach 60 million people. In general, postmenopausal women will have experience a variety of complaints such as hot flush, osteoporosis, sleep disorders, obesity, anxiety, urogenital disorders, dementia and sensory impairments. Postmenopausal women will be at risk of suffering from diabetes, coronary heart disease, osteoporosis, dementia, and cancer. Various complaints and interference are due to declining ovarian hormones including estrogen and progesterone. This situation is the reason why about 1 million postmenopausal women in the UK do hormonal replacement therapy (HRT). Reports from various overseas researchs show that HRT is useful to reduce short-term symptoms of menopause, prevent osteoporosis, and decrease the incidence of colorectal cancer, but in the long run more than 4 years should be vigilance and caution considering the negative effects such as the risk of breast cancer, uterus cancer, thromboembolism, stroke, hypertension, and biliary abnormalities. Controversy over the use of HRT is increasingly becoming debate after reports of the Women Health Initiative (WHI) in 2002 which reported an increased risk of breast cancer 1.2 time. Actually, the risk is still small compared to the risk of breast cancer because of smoking. It is therefore necessary to study the use of HRT in postmenopausal women, especially in Indonesia. Based on a qualitative study of the controversial use of HRT in menopause women among clinicians in particular medical specialist in internal medicine and a specialist gynecologist and obstetrician can be seen that clinicians tend to prefer a combination of estrogen and progesterone than estrogen singles. We found the controversy of usage HRT among clinicians into three opinion consisting pesimistic opinion, natural opinion, and conditional opinion although basically only two alternative reject or accept to use the HRT. Clinicians have more concerned about the negative effects of the risk of breast cancer in postmenopausal women who use HRT. This is due to the track record of patient incomplete, incomplete examination method to monitor the negative effects of the use of HRT, HRT dose appropriate and benefit/safety of HRT remain uncertain, and inconsistent outcomes of various research reports as well as the conflict between basic science facts role of estrogen, clinical benefit and observations epidemiological studies.

Keywords : controversy, HRT, women post menopause

Introduction

There are 470 million women aged 50 years and older living of women in the world today become menopause or post menopause (Barrett, 1993). According to WHO the numbers of post menopausal women are approximately 1.2 billion in 2020 and in Indonesia according to Central bureau of statistics there are 60 million post menopausal women in 2025 (Rambulangi, 2005). There are 75% Western post menopausal women who complained of menopause symptoms while in Asia, a study in Malaysia about the symptoms of menopause reported in 1990 that Malaysian women have no serious symptoms of menopause (Simangungson, 2009). Baziad (2003), suggests that approximately 70% of peri-menopausal women and postmenopausal women have complaints of vasomotor, depressive and psychological as well as other somatic complaints at span age of 45-54 years. Commonly a variety of complaints are hot flush, osteoporosis, sleep disorders, obesity, anxiety, urogenital disorders, dementia and sensory impairments (Zhang, 2012). Various complaints and interference are due to declining ovarian hormones including estrogen and progesterone.

Postmenopausal women have a greater risk of suffering from diabetes, coronary heart disease, osteoporosis, dementia, and cancer (Fernandes,2007; Szmuilowicz, 2009, Jenkins, 2011). Some of the conditions and the disease risk related to menopause may require medical intervention. Hormone replacement therapy (HRT) is the most commonly prescribed medicine in western medical practice. This situation is the reason why about 1 million postmenopausal women in the UK do hormonal replacement therapy (HRT). Unfortunately, despite its widely accepted benefits, the use of HRT has many potential health risks, including increased risk of breast, endometrial, ovarian cancer; increased risk of gallbladder disease; increased risk of thromboembolitic disease, and even dementia (age 65 and older). Side effects of HRT include nausea, bloating and fluid retention, and negative effects on mood. Recent research has demonstrated that long term use of estrogen more than 4 years (alone or in combination with progestin) results in more risks than benefits (Simangungson, 2009).

The current debates and controversies over HRT would suggest that serious concerns about use of HRT are a novel phenomenon especially since the reports of the Women Health Initiative (WHI) in 2002 which reported an increased risk of breast cancer 1.2 time. They also imply that current scientific awareness of possible risks associated with HRT is attributable chiefly to scientific progress, with new studies debunking old ideas (Krieger,2005). Recently many of the conclusions reached by the 2002 study, including the raised risk of breast cancer, have now been overturned. Therefore we have conducted research to reveal the controversy of usage HRT among doctors especially, general practitioner, internist and obstetrycian on practices and opinion of clinicians toward patient request to HRT as the most medical practitioner that encounter to serve menopause patients.

Methodology

Our study used qualitatif methodology by assessing the repsonse of Hospital medical committee to the clinical trial using ERT followed by interview to clinicians. Then the data will be analyzed by content analyzis to seek the most important reasoning to reject or accept the trial. After that the result we compare with literature in journal about HRT in Indonesia. Data also will be compared with opinion from academic staff and fellow of internal medicine training program (residence). This study have conducted along with the clinical trial study granted by DIKTI through *Hibah Bersaing* Project titled model of DM type 2 therapy based on polymorphism of ESR1 gene in Javanese menopausal women.

Results and Discussion

After we got ethical clearance from Bioethics Unit of Muhammadiyah University of Jogjakarta to do clinial trial HRT as additive therapy for DM type 2 in post menopause women, we have sent the letter to get permission to perform research in 4 hospital. Two hospital rejected our permission letter to do clinical trial and two hospital received our proposal. One goverment hospital rejected our proposal directly without presentation in advance and one private hospital rejected after presentation in advance. Both of two private hospital that received our clinical trial proposal have encountered presentation in advance. All reasoning why they have chosen for rejecting or accepting clinical trial shown in table 1.

According to obstetrician in RSI Klaten, the clinical trial is not safe to our patient because of using only estrogen tablet and not in line with the best evident to use combination of estrogen and progesteron.

According to internist in RSI Klaten, the time of clinical trial is too short only 6-8 week. Clinical trial is better if performed continuestly at least 4 month based on HbA1 lifetime. Also the researcher in this clinical trial proposal do not any examination to monitor the side effect especially increased risk cancer and tromboembolism. Another opinion from internist, the selection criteria of the patient was not appropriate if HRT used for addititive treatment for diabetes patient because the risk of hipogligemia if patients have taken HRT with insulin or antidiabetic tablet. The most critical consequence of the cilinical trial is after 1-3 year accomplishment of clinical trial if there is a person getting cancer what will be done by reseacher and were all patient still monitored by researcher.

Table 1. Reasoning and Decision to Clinical Trial HRT in Hospital

Hospital	Desicion	Reasoning
RSUD Kodya Jogjakarta	reject	Have no experience with clinical trial in hospital, fear with risk to the patient getting cancer
RSI Klaten	reject	Violate patient safety and controversy of the benefit
RSI Kalasan	accept	tight selective treatment
RSU Kharisma Wates	accept	Should consult with internist and obstetrician to select the most appropiate patient to get safety

Regarding clinical trial of HRT in Indonesian menopause women is still difficult because of lack of understanding about HRT in short term and long term effect. Rejection decision did not base on scientific background but based on assumption only because of no experience before. According to Ministry of Health of Indonesia in 2004, Research on the use of hormone replacement therapy is generally performed on women Caucasian race. Demographic differences, race, lifestyle, and culture among women western countries with Asian women need to lead a review of the use of hormone replacement therapy in Indonesia, which includes indications, type, dosage and safety. In the risk-benefit balance is reported, the risk of the use of hormone replacement therapy for primary and secondary prevention of chronic diseases related to menopause, overall outweighs the benefits obtained.

Regarding patient request on HRT, some doctors opinion have shown in table 2. Obstetrician have opinion much more wise than other clinicians. That's way other clinicians have frequently preferred to consult and sometimes refer his menopause women to obstetricians to get HRT. Basically all problems of menopause women have related to lack estrogen. This biochemical basis of low estrogen-related disease has become simple consideration to give treatment HRT but pleiotropic effect exists in the some organs resulting HRT harm outweighed its benefit. Obstetrician opinion that estrogen-progesterone combined is better than estrogen only have become controversy because progesterone has given benefit only for reducing endometrium cancer than single estrogen and also increase risk venous thrombi embolic (VTE) to patients and increase of ovarian cancer incident.

Table 2. Attitude doctors toward patient request HRT

Informant	Attitude	Reasoning
Residence	Reject and refer to Obstetry	Have no experience in treatment
Internist	Reject	Natural process no need any medication and better by lifestyle adaptation
Obstetrician of academic staff	Accept	With carefull consideration and consultation if no history of cancer and better using phyto estrogen or vitamin E
General practitioner	Accept	Depend on menopause symptom and complaint but just for short periode
Academic staff	Accept	balancing the patient condition if decreased estogen as main factor of symptom
Obstetrician in hospital	Reject for estrogen only Accept for combination HRT	estrogen only of HRT is out of date and more harmful than combination HRT

We found the controversy of usage HRT among clinicians into three opinion consisting pesimistic opinion, natural opinion, and conditional opinion although basically only two alternative reject or accept to use the HRT. Pesimistic opinion just have consider negative effect of HRT for menopuase women based on instant information that HRT will increase 1.2 times to get breast cancer. This opinion is weak because the risk of geting breast cancer is not only effect of HRT but also from genetic factor. According to van der Hel *et al.* Genetic factors, acquired environmental factors or, most often, a combination of both probably causes breast cancer (Van der Hel, et. al, 2003). A family history of breast cancer and several reproductive characteristics are acknowledged risk factors. For smoking, the results are less conclusive, although Khuder et al.[12] summarized 40 studies and showed a 10% higher risk for women who ever smoked [pooled relative risk ¼ 1.10; 95% confidence interval (CI) 1.02–1.18] (Khuder, 2001).

Another recent meta-analysis suggests no relation between smoking and breast cancer overall (Anonim, 2002). However, there may be women who are more susceptible for smoking compared to other individuals because of their genetic make-up. Cigarette smoke contains rodent mammary carcinogens, such as polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines and heterocyclic amines. Individual cancer susceptibility following exposure to these tobacco carcinogens may be based on differences in the capacity of metabolic enzymes to activate or deactivate the carcinogens and form DNA adducts. According to van der Hel *et al.* Compared to never smoking, smoking 20 cigarettes or more per day increased breast cancer risk statistically significant only in postmenopausal women [odds ratio (OR) 2.17; 95% confidence interval (CI) 1.04–4.51].[11] This condition may become important lesson to researcher about genetic background as contributing factor that increase the risk of breast cancer in post-menopausal women. The results of van der Hel *et al.* provide support for the view that women who smoke and who have a genetically determined reduced inactivation of carcinogens (GSTM1 null genotype or slow NAT2 genotype (especially very slow NAT2 genotype)) are at increased risk of breast cancer (Van Der Hel, 2003). The controversy of HRT as risk factor of breast cancer is similar with smoking as risk factor of breast cancer but opinion of the role of HRT as risk factor of breast cancer could be much more sensitive.

Pessimistic opinions also have no consideration time of consuming of HRT so that consumption in short term less than 1 year may be supposed to increase risk of breast cancer. In deed the time should at least 5 years in consuming of HRT. Pessimistic opinions have built from data that HRT users may increase 2 persons with breast cancer in 1000 women as long as 20 years usage.[16] Pessimistic opinion of clinicians have more concerned about the negative effects of the risk of breast cancer in postmenopausal women who use HRT. Increasing knowledge of HRT for clinicians are important to minimize pessimistic view especially on specialist training program and undergraduate program of medical faculty. By increasing knowledge the best women and their doctors can do is to try to scrape away as much mud as possible - to sort out what we know and what we don't know - and take their best guess.

Natural opinions are similar with pessimistic opinion in rejecting HRT but differ in treatment. Natural opinions may active to help patient by self-management to change lifestyle and use phytoestrogen. Pessimistic opinions have no treatment and no behavior intervention. Natural opinions are much more responsible to handle symptom of menopause by consultation. Natural opinions have basic reasoning according to natural history disease. Based on data over 20 years of menopause women from 50-70 years age there are 45 women getting breast cancer without HRT treatment (Pherson, 200).

Conditional opinions have to accept HRT with prerequisite and will reject if the prerequisite is not fulfilled. The prerequisite includes the complete history of disease of patient, complete family history of disease, well educated, laboratory assessment for balancing the risk such as mammography, FSH/LH and estrogen examination, profile lipid, blood coagulation test, and other data of BMI, smoking, radiation, and diets or lifestyle. Conditional opinion is safe opinion because there is no experiment report using clinical trial of HRT in menopause women in Indonesia. Based on conditional opinions there are examinations that must be met prior to hormone replacement therapy such as definitive diagnosis of menopause, assessment of absolute and relative contraindications, informed consent regarding the advantages and disadvantages of the use of hormone replacement therapy, physical examination, including blood pressure, breast and pelvic examinations and cervical cytology and mammography should give negative results. Caution should be paid attention for establish and probable risk factor such as age (elderly >10 times risk to breast cancer), developed country (>5 times risk to breast cancer), age at menarche before 11 (>3), age at menopause >54

(>2), age at full preganancy (>3), family history of first relative degree getting breast cancer (≥2), previous benign disease (>4-5), cancer in other breast (>4), socio economic group (>2) and diets (>1.5) (Lloyd's, 2008).

The last statement issued by the Women's Health Initiative (WHI) and the Heart and Estrogen / Progestin Replacement Trial (HERS) states that there is an increased risk for CHD, stroke and breast cancer in hormone replacement therapy use in a certain period of time, so it takes a review re-use in postmenopausal women. Actually, it is possible to experience a variety of chronic diseases during his expected 46% for CHD, 20% for stroke, 15% for hip fractures, 10% for breast cancer, and 2.6% for endometrial cancer. In North America, as many as 7-8% of people aged 75-84 years of developing dementia of Alzheimer's type and postmenopausal women had 1.4-3 times the risk for Alzheimer's disease than men, whereas the risk for colorectal cancer is approximately 6% where more 90% of cases occur after the age of 50 years. Mortality and morbidity occurred in this case reported to be associated with the pathophysiology of the disease based on the low levels of estrogen and progesterone body (Anonim, 2004). Normally there is controversy of increased natural risk of disease because of aging and increase of artificial risk because of HRT treatment. The controversy may be due to the track record of patient incomplete, incomplete examination method to monitor the negative effects of the use of HRT, HRT dose appropriate and benefit/safety of HRT remain uncertain, and inconsistent outcomes of various research reports by different population in various region as well as the conflict between basic science facts role of estrogen, clinical benefit and observations epidemiological studies.

The American College of Obstetrics and Gynaecologists (ACOG) have established contra indications for hormone replacement therapy, i.e. pregnancy, genital bleeding of unknown cause, acute or chronic liver disease, diseases of vascular thrombosis and patient refused treatment. ACOG also have established relatively contraindicated, hypertriglyceridemia, history of thromboembolism, history of breast malignancy in the family, disorders of gallbladder, migraine, uterine myomas and seizure disorder (Mc Nagny, 1999).

The Hong Kong College of Obstreticians and Gynaecologists mention a few absolute contraindications to HRT, the breast carcinoma, endometrial cancer, a history of venous thromboembolism and acute liver disease (Anonim, 2003). Women are currently advised to take HRT only if their symptoms are severe, and to use it for as short a time as they can tolerate. Women who have a history of breast, uterine and ovarian cancer, or a high risk of developing them, vaginal bleeding for unknown reason, liver disease, thromboembolism or cardiovascular disease, are not recommended to take HRT.

To make convenience and get best result, clinicians should give recommendation based on hierarchy of evidence as follows :

Ia. Meta-analysis of randomized controlled trials.
Ib. At least one randomized controlled trials.
IIa. Minimal research non-randomized controlled trials.
IIb. Cohort and Case control studies
IIIa.Cross-sectional studies
IIIb.Case series and case reports
IV. Degree of consensus and expert opinion and advice:

Degree of recommendations:

A. Evidence included in the level Ia and Ib.
B. Evidence included in level IIa and II b.
C. Evidence included in level IIIa, IIIb and IV.

Degree of recommendation grade A (Ia level) is pointed out HRT for treatment menopause symptom as long as 3 month or 3 years using micronized estradiol. Grade A recommendation of HRT (level Ia) also has been suitable for reducing osteoporosis post menopause using oral equine estradiol 0,625 mg or less as long as 5 years. Profile lipid has also become much better using equine estrogen conjugate (EEC) for at least 2 weeks. Grade A of HRT is to improve profile lipid but not for cardiovascular disease. Grade A has become recommendation for preventing colorectal cancer but grade A recommendation has not suggested for preventive cardiovascular disease, stroke and dementia. Grade B recommendation has suggested to prevent dry eyes syndrome.

Estrogen only of HRT can reduce breast cancer and endometrium cancer compared with estrogen and progesterone combination. This recommendation is grade A also. HRT may increase VTE so not recommended to patients with thrombosis risk and estrogen-progesterone combined

double the risk VTE than single estrogen. For decades, researchers, physicians, and women's health advocates have debated the risks and benefits of estrogen, with or without progestin. In the 1950s and 1960s, when Ayerst Laboratories aggressively began marketing their estrogen preparation, Premarin, supplementary hormones for postmenopausal women were heralded as a panacea that would, in the seductive words of New York gynecologist Robert Wilson, keep women "feminine forever." Yet, by the 1980s, various critics began arguing that supplementary hormones were a serious and unnecessary risk to women's health.

The critics' greatest concern was breast cancer, a disease that many women understandably fear (although heart disease causes far more deaths than breast cancer does) (Bluming, 2009). In Indonesia the premarin tablet is not available any more because of controversy the use of HRT. Recently what we know that the smallest required dose is given for the shortest amount of time and low risk for age below 60 years old and not difference at < 70 years old (Anonim, 2004).

Conclusion

Controversy of the use of HRT consist of three opinion/view namely pessimistic opinion, natural opinion and conditional opinion although only two attitude rejecting or accepting of HRT clinical trial in hospital. Clinicians still need more knowledge and information about HRT to reject or accept patient request on HRT. Obstetricians are more prominent in HRT for menopause women than others. In this first preliminary study of HRT controversy in Indonesia need advance study that involved many clinicians and hospital/clinic as well as faculty of members. Clinicians have more concerned about the negative effects of the risk of breast cancer in postmenopausal women who use HRT

Acknowledgement

This study was financially supported by Direktorat Jenderal Pendidikan Tinggi Kementrian Pendidikan Nasional Republik Indonesia through HIBAH BERSAING research grant 2012.

References

Barrett-Connor E., 1993. Epidemiology and the menopause_a global overview. *Int J Fertil Menopausal Stud.*, 38(Suplll 1), pp.Suplll 6–14.

Rambulangi J., 2005. Challenges, Hope and Alternative Medicine In. Improving Productivity and Quality of Life Women's Menopause. Supplement 26 (3);98-102

Simangungson, D.E., 2009. Relationship characteristics of perimenopausal women with health services in the city of Pematang Siantar in 2009. Graduate School of USU (Thesis), Medan

Baziad, 2003. Menopause and andropause. 1th edition, Bina Pustaka Sarwono Prawirohardjo, Jakarta.

Zhang, X.Y., Traditional Chinese Medicine (TCM) in the Management of Menopausal Symptoms / Conditions. *Women's Health Clinic, London, UK.* Available at: http://www.womenshealthclinic.co.uk/TCMMenopause.pdf [Accessed October 14, 2012].

Fernandes, L. & Lara, J., 2007. Cardiovascular disease and in osteoporosis: Coronary artery disease women: a review Balancing risk management on prevention , pathophysiology , diagnosis , and treatment. *Vasc Health Risk Manag.*, 3(5), pp.673–690.

Szmuilowicz, E.D., Stuenkel, C. a & Seely, E.W., 2009. Influence of menopause on diabetes and diabetes risk. *Nature reviews. Endocrinology*, 5(10), pp.553–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19687788 [Accessed September 3, 2012].

Jenkins, B.W.C. et al., 2011. Association of the Joint Effect of Menopause and Hormone Replacement Therapy and Cancer in African American Women: The Jackson Heart Study. *Int. J. Environ. Res. Public Health*, 8, pp.2491–2504.

Victor W. Henderson, 2009. Cognitive Changes After Menopause : Influence of Estrogen. *Clin Obstet Gynecol.*, 51(3), pp.618–626.

Krieger, N. et al., 2005. Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. , pp.740–748.

Van der Hel, O.L.et al., 2003. NAT2 slow acetylation and GSTM1 null genotypes may increase postmenopausal breast cancer risk in long-term smoking women. *Pharmacogenetics*, 13(7), pp.399–407.

Khuder SA, Mutgi AB, Nugent S. 2001. Smoking and breast cancer: a metaanalysis. Rev Environ Health 16:253–261.

Anonim, Collaborative Group on Hormonal Factors in Breast Cancer. 2002. Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. Br J Cancer 87:1234–1245

Bluming, A.Z. & Tavris, C., 2009. Hormone Replacement Therapy : Real Concerns and False Alarms. *The Cancer Journal*, 15(2), pp.93–104.

Anonim, Ministry of Health (MOH) RI, 2004. Hormone replacement therapy in women perimenopuase. Health Technology Assessment ; pp 1-47

Pherson, K.Mc., Steel, C.M., Dixon, J.M., 2000. *ABC of Breast Diseases ;* Breast cancer—epidemiology, risk factors, and genetics. BMJ 321;624-628

McNagny SE. 1999. Prescribing hormone replacement therapy for menopausal symptoms. Ann.Intern Med.131;606-15

The Hong Kong College of Obstetrician and Gynaecologists. Guidelines for the administration of hormone replacement therapy. January, 2003. *Available at:* http://www.hkcog.org.hk/docs/guidelines

Lloyd's, 2008. Hormone replacement therapy An overview of the risks of hormone replacement therapy. Lloyd's emerging risks team report. the Franchise Performance Directorate at Lloyd's. *Available at:* http://www.lloyds.com/emergingrisks.