Executive Board
of
The Royal Thai College of Obstetricians and Gynaecologists

PRESIDENT

Prof. V. Titapant, M.D.

PRESIDENT-ELECT

Prof. S. Wilailak, M.D.

EXECUTIVE BOARD MEMBERS

Assoc. Prof. A. Jaishuen, M.D.
Assoc. Prof. A. Kamudhamas, M.D., DHS, Ph.D.
Assist. Prof. A. Yantapant, M.D.
Assoc. Prof. B. Chumworathayi, M.D., Ph.D.
Assoc. Prof. C. Wanapirak, M.D.
Assoc. Prof. K. Panyakhamlerd, M.D.
Assoc. Prof. M. Thamkhantho, M.D.
Assist. Prof. N. Israngura Na Ayudhya, M.D.
O. Musigavong, M.D.
Assoc. Prof. P. Ruangvutilert, M.D., Ph.D.
Assoc. Prof. S. Bunyavejchevin, M.D.
S. Khunpradit, M.D.
Assoc. Prof. T. Suntharasaj, M.D.
Assoc. Prof. W. Termrungruanglert, M.D.

Thai Journal of Obstetrics and Gynaecology

ISSN : 0857-6084. The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

Editor in Chief

PHUPONG Vorapong

King Chulalongkorn Memorial Hospital, Chulalongkorn University, Thailand

Editorial Board:

Manager: Prof. Vitaya Titapant, M.D.
Assistant Manager: Arissara Puangmalee
Office: 8th Floor, The Royal Golden Jubilee Bldg. 2, Soi Soonvijai, New Petchburi Road, Bangkapi, Bangkok 10310, Thailand
Published by: PIMDEE Co., Ltd. Tel: 091-009-4011 Fax: 0-2874-4401,

Aim and Scope of the Thai Journal of Obstetrics and Gynaecology (Official journal of the Royal Thai College of Obstetricians and Gynaecologists (RTCOG)

Thai Journal Obstetrics and Gynaecology (TJOG) is the official journal of The Royal Thai College of Obstetricians and Gynaecologists (RTCOG). This is a double-blind peer-reviewed journal aiming to promote academic knowledge and provide a forum for publication in Obstetrics and Gynecology. Manuscripts submitted to TJOG will be accepted on the understanding that the author must not have previously submitted the paper to another journal or have published the material elsewhere.

Type of Paper: Special (invited) article, Original article, Case report
Frequency: 4 issues per year (January-March, April-June, July-September, October-December)
Language: Fulltext in English, Abstract both in Thai and English
Free Access: online
ISSN: 0857-6084 (Since 1989)
E-ISSN: 2673-0871 (Since December 2010)

Peer Review Process

TJOG has double-blind peer-review process. The editorial board consists of professor, associate professor and assistant professor in fields of Obstetrics and Gynaecology, who have experience in conducting and publishing research. At least two reviewers evaluate manuscript. Initial reviews usually accomplish within 4 weeks.

Publication Charges

To publish in Thai J Obstet Gynaecol, authors are required to pay publication charge. The publication charge for all published papers is US$100/paper after official acceptance. Payment for publication does not affect peer review process.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Subscription

For hard copy subscription, the annual subscription rate is US$ 50.

Sponsor and Source of Support

RTCOG

Journal History

TJOG is the official journal of RTCOG. This is a double-blind peer-reviewed journal aiming to promote academic knowledge and provide a forum for publication in Obstetrics and Gynecology. First issue of TJOG (Volume 1) was published in June 1989.

Improvement of TJOG has been documented. TJOG was accepted for indexing by the Thai Journal Citation Index (TCI) in December 2010 and indexed in the ASEAN Citation Index (ACI) in September 2015. TJOG also received the National Journal Award from the 3rd TCI-Scopus-TRF Journal Awards on December 15, 2016.

Direction to contributors. All papers should be sent to Editor, Thai Journal of Obstetrics and Gynaecology by online submission. The editorial board will decide upon the time of publication and retain the right to modify the style and the length of the contribution. However, major changes will be agreed with the authors.

Manuscripts. All manuscripts can be submitted online (https://tci-thaijo.org/index.php/tjog) along with a cover letter, author agreement form and the checklist guideline. A cover letter must include name of the corresponding author, full address, telephone number, fax number, and e-mail address, title and category of the submitted manuscript: original article, case report or review articles. Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English.

The requirements for manuscripts submitted to TJOG conform to the UNIFORM REQUIREMENT FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS established by the international committee of medical journal editor which published in N Engl J Med 1991;324:424-8 and BMJ 1991;302:338-41.

Manuscripts of original work should be arranged in the conventional order of title page, abstract, keywords, introduction, materials and methods, results, discussion, acknowledgments, references, table and figure legends.

Manuscripts of research article, case report and review article (without author's name) will be reviewed by two reviewers. Editor in chief will make the final decision in case of discrepancy of reviewer's opinion. The editorial board has the right to grammatically correct any content and has all right preserved to consider and to publish any article.

All published manuscripts are properties of TJOG. The content and any opinions in the published papers are the sole responsibility of the authors, not the editorial board.

Title page. The title page should contain the title, which should be concised and informative, the authors' name with the highest academic degree, and address of the authors including the correspondence.

Abstract. A structured abstract, with 250 words or less, is submitted as required for regular articles. The abstract should state the Objective, Materials and Methods, Results, and Conclusion, each with a brief adequate presentation. Abstracts for case reports should not exceed 150 words.

Keyword. Below the abstract list 3 to 5 keywords or short phrases for indexing purposes.

Introduction. State clearly the purpose of the study. Summarize the rationale for the study. Give only strictly pertinent references and it is not necessary to include all the background literature.

Materials and Methods. Describe briefly the plan, patients, procedures, controls and statistical method employed.

Results. Present your results in sequence in the text, tables, and illustrations. Summarize and emphasize only important observations.

Discussion. Comment on your results and relate them to those of other studies. Recommendations may be included.

References. References to the literature should be numbered consecutively and indicated by a superscript in parenthesize. Identify references in the text, tables and legends by arabic numerals within marks. Cite the names of all authors when there are six or fewer; when seven or more list the first six followed by et al. Names of journals should be abbreviated in the style used in Index Medicus. Try to avoid using abstracts as references. Unpublished data and personal communication should not be used as references. The reference style of Thai J Obstet Gynaecol from EndNote® program can be download here.

Example of references:

Journal article

Phupong V, Aribarg A. Congenital arteriovenous malformations of the uterus. Thai J Obstet Gynaecol 2000;12:67-70.

Book

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams Obstetrics. 23rd ed. New York: McGraw-Hill, 2010: 804-31.

Chapter in a Book

Phupong V. Management of PPROM AT 32 to 34 weeks. In: Desai SV, Tank P, eds. Handbbok on preterm prelabor rupture of membranes in a low source setting. New Delhi: Jaypee Brothers Medical Publishers Ltd, 2012: 39-46.

Tables. Tables should present new information rather than duplicating what is in the text. Please supply editable files. A short descriptive title should appear above each table with a clear legend and any foonotes suitably identified below. All units must be included.

Figures. Figures should be high quality (1200 dpi for line art, 600 dpi for gray scale and 300 dpi for colour). Figures should be saved as TIFT or JPEG files. Figures should be completely labelled, taking into account necessary size reduction. Captions should be typed, double - spaced, on a separate sheet.

Publication Ethics and Publication Malpractice Statement.

The publication ethics is required for publication in TJOG (Thai J Obstet Gynaecol). The publication ethics guidelines are guided by the Committee on Publication Ethics-(COPE).

Editors of Thai Journal of Obstetrics and Gynaecology

- attempt to meet the demand of readers and authors, improve the quality of the journal, and have processes in place to assure the quality of the material published, seek the opinions of authors, readers, reviewers and editorial board members about the ways to improve the journal's processes and maintain the integrity of the academic record and preclude business needs from intellectual and ethical standards.
- have a duty to act if editors suspect misconduct or if a misconduct is documented, pursue misconduct for the following reasons in published and unpublished work: plagiarism, data fabrication and falsification, when a submitted article has been found to be under revision elsewhere or published elsewhere, or where there is citation manipulation, and are willing to publish corrections, clarifications, retractions and apologies when needed.
- seek assurances that all research has been approved by research ethics committee or institutional review board, and ensure that research published was carried out according to the relevant internationally accepted guidelines such as the Declaration of Helsinki for clinical research
- give timely and constructive feedback to authors, respect requests from authors that an individual reviewer should not review their submission if these are well reasoned, make decisions to accept or reject an article for publication based on the article's importance, originality and clarity, and the study's validity and its relevance to the remit of the journal.

Authors who submit articles to Thai Journal of Obstetrics and Gynaecology should

- follow to publication requirements that their submitted article is original, is not plagiarized, and has not been published elsewhere, and take the responsibility for submitted and published article.
- confirm that the authorship of research publications accurately reflect authors' contributions to the work and reporting, and disclose sources of funding and conflicts of interest.
- present the research conducted in an ethical and responsible manner and comply with all relevant legislation, describe the methods clearly so that the findings can be confirmed by others, present the results clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

Reviewers of Thai Journal of Obstetrics and Gynaecology should

- agree to review the article which they have the expertise

and can assess in a timely manner, and respect the confidentiality of peer review and not reveal any details of an article or its review except the release by the journal

- declare all potential conflict of interests, not allow their reviews to be influenced by the following items: the origins of an article, the nationality, the religious or political beliefs, the gender of the authors, or commercial considerations

- have objective and constructive comments in their reviews, and provide the journals with personal and professional information that is accurate from their expertise

Publication Decisions

Thai Journal of Obstetrics and Gynaecology will not accept articles which have been published (except in the form of an abstract) or are being considered for publication by another journal. Papers being considered for publication here should not be submitted to other journals.

The editor of Thai Journal of Obstetrics and Gynaecology is responsible for deciding which of the articles submitted to the journal should be published. The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements regarding libel, copyright infringement and plagiarism. The editor may confer with editorial board or reviewers in making this decision.

Plagiarism

Intellectual property is seriously concerned by TJOG. On submission, all articles are screened using the 'HelioBLAST' (https://helioblast.heliotext.com). Any plagiarism is unacceptable. The Editor-in-Chief will be informed. Plagiarism results in rejection. If plagiarism is detected during reviewing process by any means, all the process will be immediately withheld. The Editor-in-Chief will contact the corresponding author and/or all authors for explanation. Rejection of submission will occur once the explanation is unsatisfactory. If plagiarism is detected after publication, the article will be retracted. All the authors' institutions will be contacted to explain the retraction and inform the expected future behaviours. The event of retraction will be officially announced in the Journal.

Thai Journal of Obstetrics and Gynaecology

The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

ISSN 0857-6084 E-ISSN 2673-0871

Vol. 30 No. 2 MARCH - APRIL 2022

CONTENTS

EDITORIAL

Phupong V..... 77

SPECIAL ARTICLE

Confounding Factors in Noninvasive Prenatal Testing under Common Benign Gynecologic Conditions
Hanprasertpong T..... 78

ORIGINAL ARTICLES

Accuracy of 12-hour versus 24-hour Urine Collection for Diagnosis of Preeclampsia
Sarnnok S, Kitiyodom S..... 82

Comparing the Efficacy in Reducing Pelvic Pain Score at 3 Months after Treatment in Clinically Diagnosed Endometriotic Patients between Leuprolide Acetate and Depot Medroxyprogesterone Acetate, A randomized controlled trial
Sowannakul A, Kiettisanpipop P, Kongsomboon K..... 91

Effect of Electric Breast Pump versus Conventional Breastfeeding on Onset of Lactation in Post-cesarean Women: A randomized controlled trial
Muangban S, Jeerasap R, Tangsiriwatthana T..... 100

Hot Patch Applied to the Lower Back for Pain Relief during the Active Phase of the First-stage Labor: A randomized controlled trial
Suthisuntornwong C, Tangsiriwatthana T..... 109

Lidocaine Prilocaine Cream in Conjunction with Paracervical Block versus Placebo with Paracervical Block for Pain Relief during Fractional Curettage
Duangrudeesawat B, Srinil S..... 120

Quality of Life after Treatment by Vaginal Pessary versus Surgery in Symptomatic Pelvic Organ Prolapsed Thai Patients
Panjapong S, Buppasiri P, Chongsomchai C, Temtanakitpaisan T..... 128

Urinary Incontinence: Women Attending the Gynecology Outpatient Clinic Unaware of Symptoms
Srisanam M, Buppasiri P, Chongsomchai C, Temtanakitpaisan T..... 136

CASE REPORT

Diagnosis of Pentalogy of Cantrell with Craniorachischisis at 11weeks on 2 Dimensional Ultrasound - A rare case report
Inukollu PR, Bhavana SD, Gupta S, Solipuram D, Shyamala G..... 145

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 77

EDITORIAL

This second issue of Thai Journal of Obstetrics and Gynaecology (TJOG) 2022 contains many interesting articles. One special article is "Confounding Factors in Noninvasive Prenatal Testing under Common Benign Gynecologic Conditions".

Editor in Chief and managing staff of TJOG already attended "Introducing the new ThaiJO2.0 system." on 18 February 2022. Editorial Board of TJOG looks forward to continuously raising the quality of the TJOG.

The Royal Thai College of Obstetricians and Gynaecologists (RTCOG) midyear meeting 2022 will be held during 26-29 April 2022 at Dusit Thani Hua Hin Hotel, Phetchaburi, Thailand. The theme of this meeting is "Talking OB-GYN 2022". All RTCOG members are cordially invited to participate this scientific meeting.

Due to the high number of COVID-19 infected cases, all RTCOG members please keep yourself and others safe from COVID-19: social distancing, maintain at least a 1-metre distance, make wearing a mask a normal part, regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water, avoid touching your eyes, nose and mouth, cover your mouth and nose with your bent elbow or tissue when you cough or sneeze, and avoid crowded or indoor settings.

Wish to see you at RTCOG midyear meeting 2022 at Dusit Thani Hua Hin Hotel, Phetchaburi, Thailand.

Wish all RTCOG members and families safe from COVID-19.

Prof. Vorapong Phupong, M.D.
Editor in Chief

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 78-81

SPECIAL ARTICLE

Confounding Factors in Noninvasive Prenatal Testing under Common Benign Gynecologic Conditions

Tharangrut Hanprasertpong, M.D.*

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhorn Nayok, Thailand*

ABSTRACT

Noninvasive prenatal testing (NIPT) is increasing in use in obstetric practice worldwide, including in Thailand. While the efficacy of NIPT for prenatal aneuploidy detection is accepted, there are some pathologic conditions that can interfere with the NIPT result, such as maternal autoimmune disease or malignancies. Interestingly, some common benign gynecologic conditions, including uterine myoma, endometriosis, and mature ovarian cystic teratoma, have been reported to be confounding effects of maternal cell-free dexoxy ribonucleic acid (DNA) on the NIPT result.

Keywords: noninvasive prenatal testing (NIPT), cell-free DNA (cf-DNA).

Correspondence to: *Tharangrut Hanprasertpong, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhorn Nayok 26120, Thailand. Email: tharangrut @hotmail.com, tharangrut@gmail.com*

Received: 21 September 2021, **Revised:** 25 November 2021, **Accepted:** 30 November 2021

Noninvasive prenatal test

Noninvasive prenatal testing (NIPT) is a modern modality to prenatally screen fetal chromosomal abnormalities. It has been widely implemented in obstetric practice due to its high accuracy and proven clinical validity[1]. NIPT offers intermediate efficiency for prenatal aneuploidy detection, lying between biochemistry serum screening and invasive prenatal diagnostic testing[2]. In Thailand, a previous recent study reported that 91.1% of pregnant women agreed to participate in Down syndrome screening[3]. NIPT can be applied to analyze the fetal aneuploidy risk from fetal cell-free dexoxy ribonucleic acid (cf-DNA) fragments circulating in the maternal blood. Such fetal cf-DNA is derived from apoptotic cytotrophoblasts and it remains in maternal circulation for a few days after delivery[4]. After maternal blood sample collection, the cf-DNA can be extracted and processed for DNA sequencing using shotgun massively parallel sequencing (MPS). Then the sequencing data can be analyzed and compared with a sample obtained from the maternal euploid fetus. An under-presentation or over-presentation of calculated Z-scores is reported as a suspected indication of the fetus being affected by monosomy or trisomy, respectively. However, non-reportable results are shown in some situations. A possible cause of a non-reportable NIPT result is an

insufficient fetal fraction, which may be caused by too early gestation or the effect of a large maternal weight[5]. Besides an insufficient fetal fraction, cf-DNA originating from maternal apoptotic white blood cells and maternal neoplastic cells can be represented in the NIPT result and therefore can interfere in the NIPT analysis[6]. Both epithelium and germ cell malignant ovarian neoplasm have been reported to result in false-positive or non-reportable results for NIPT[7-8]. Moreover, non-gynecologic malignancy, such as gastric cancer, has been also identified during NIPT[8].

Detection of circulating cf-DNA in common cenign gynecologic neoplasm

Uterine leiomyoma, endometriosis, and mature ovarian cystic teratoma are common benign gynecologic diseases. The prevalence of uterine leiomyoma during pregnancy has been reported to be approximately 1.6% to 10.7%, depending on the trimester and method of assessment[9]. Usually, uterine leiomyomas are asymptomatic during pregnancy[10]. Endometriosis is a chronic gynecologic disorder, with a prevalence in all reproductive-age women of around 1% - 2%, who commonly present with infertility, dysmenorrhea, chronic pelvic pain, and dyspareunia[11]. Although infertility is associated with endometriosis, pregnancy can still successfully occur after treatment. Mature ovarian cystic teratoma is usually benign and asymptomatic during pregnancy. The incidence of complicated mature ovarian cystic teratoma during pregnancy, such as torsion, is approximately 15% and it occurs more frequently at 10-17 weeks' gestation[12]. A finding of circulating cf-DNA arising from uterine leiomyoma, endometriosis, and mature ovarian cystic teratoma has been previously reported[6, 13–15]. Circulating cf-DNA originating from maternal cells is called maternal cf-DNA. Analyzed cf-DNA in NIPT has been found to be a mixture of maternal and fetal cf-DNA. Thus, chromosomal copy-number alteration (CNA) of a maternal origin can lead to the NIPT calculated Z-score to show an under-presentation or over-presentation[15].

Confounding factors in NIPT by common benign gynecologic diseases

Non-reportable NIPT is documented when a questionable Z-score is observed. There are several observed Z-score characteristics of NIPT in pregnant women affected by common benign gynecologic diseases, such as[15]:

1. A highly negative Z-score of an autosome, indicating an under-presentation of the Z-scores and suggesting a suspected autosomal chromosome. Most embryos/fetuses with autosomal monosomy or sex chromosomes (lack of one member of a chromosome pair) are not viable. Only some individuals with monosomy of the sex chromosomes (45XO, Turner's syndrome) or partial autosomal monosomy can survive [16].

2. The observation of multiple chromosomal and/or subchromosomal region abnormalities[13], such as abnormal Z-scores for both chromosomes 21 and 18. It is rare for a single fetus to survive with multiple trisomies, especially at an advanced gestational age.

3. The combination indicates an increase (over-presentation) for some genomic regions and a reduction (under-presentation) for others[15].

Clinical suggestions when a confounding NIPT result by common benign gynecologic diseases is suspected

Until now, the clinical importance of a confounding NIPT result by common gynecologic conditions is still controversial. The prevalence of non-reportable NIPT in pregnancy with the presence of uterine myoma has been reported to be approximately 3.75 cases per 100,000 pregnancies[15]. The reasons for the low prevalence can be hypothesized as follows: [i] Only 7 in 13 (54%) leiomyoma hysterectomy or myomectomy specimens

have a clonal chromosome rearrangement detected. The most common chromosomal aberrations in uterine myomas are translocation, which means they should not interfere with the calculated Z-score in the NIPT process[17]; [ii] maternal cf-DNA from a small size tumor with low blood supply is low enough to detect in the NIPT process[15]. Moreover, data on chromosomal aberrations in endometriosis and mature ovarian cystic teratoma are limited. There are few case reports that have found confounding cf-DNA in maternal blood[11-12]. However, the significance of the data remains limited and needs further investigation.

Conclusion

In conclusion, NIPT in pregnancy with benign gynecologic diseases, including uterine myoma, endometriosis, and mature ovarian cystic teratoma, still offers more benefits than the risk of non-reportable results. However, proper pre-test counseling about the non-reportable results should be provided. In contrast, if a non-reportable result is shown in NIPT, the obstetrician should carefully evaluate the causes of the non-reportable result, including the Z-score characteristic, which may be influenced by a maternal confounding cf-DNA arising from common benign gynecologic diseases. Detailed ultrasonographic scanning as part of a pelvic organ survey should be performed and a prenatal diagnostic procedure, such as amniocentesis, may be indicated. Finally, further study is warranted with an adequate sample size to reveal the incidence of confounding cf-DNA from maternal common benign gynecologic diseases.

Potential conflicts of interest

The author declares no conflicts of interest.

References

1. Taylor-Phillips S, Freeman K, Geppert J, Agbebiyi A, Uthman OA, Madan J, et al. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndrome: a systematic review and meta-analysis. BMC Open 2016;6:e010002.
2. Allyse M, Minear MA, Berson E, Sridhar S, Rote M, Hung A, et al. Non-invasive prenatal testing: a review of international implementation and challenges. Int J Womens Health 2015;7:113-26.
3. Vanitchanont M, Hemachandra A. Factors affecting the decision to participate in Down syndrome screening of pregnant women at HRH Princess Maha Chakri Sirindhorn Medical Center. Thai J Obstet Gynaecol 2020;28:206-16.
4. Hochstenbach R, Nikkels PG, Elferink MG, Oudijk MA, van Oppen C, van Zon P, et al. Cell-free fetal DNA in the maternal circulation originates from the cytotrophoblast: proof from an unique case. Clin Case Rep 2015;3:489-91.
5. Hudecova I, Sahota D, Heung MM, Jin Y, Lee WS, Leung TY, et al. Maternal plasma fetal DNA fractions in pregnancies with low and high risks for fetal chromosomal aneuploidies. Plos One 2014;9:e88484.
6. Dharajiya NG, Grosu DS, Farkas DH, McCullough RM, Almasri E, Sun Y, et al. Incidental detection of maternal neoplasia in noninvasive prenatal testing. Clin Chem 2018;64:329-35.
7. Cohen P, Flowers N, Pertile MD, Hannan N, Tong S, Hui L. Detection rates of high grade serous ovarian cancers using a clinical non-invasive prenatal testing platform: potential for ovarian cancer screening. Ultrasound Obstet Gynecol 2016;48(Suppl 1):1-50.
8. Dharajiya NG, Grosu DS, Farkas DH, McCullough RM, Almasri E, Sun Y, et al. Incidental detection of maternal neoplasia in noninvasive prenatal testing. Clin Chem 2018;64:329-35.
9. Qidwai GI, Caughey AB, Jacoby AF. Obstetric outcomes in women with sonographically identified uterine leiomyomata. Obstet Gynecol 2006;107:376-82.
10. Strobelt N, Ghidini A, Cavallone M, Pensabene I, Ceruti P, Vergani P. Natural history of uterine leiomyomas in pregnancy. J Ultrasound Med 1994;13:399-401.
11. Miura M, Ushida T, Imai K, Wang J, Moriyama Y, Nakano-Kobayashi T, et al. Adverse effects of endometriosis on pregnancy: a case-control study. BMC Pregnancy Childbirth 2019;19:373.
12. Baradwan S, Sendy W, Sendy S. Bilateral dermoid ovarian torsion in a young woman: a case report. J Med Case Rep 2018;12:159.
13. Lenaerts L, Van Calsteren K, Che H, Vermeesch JR, Amant F. Pregnant women with confirmed neoplasms should not have noninvasive prenatal testing. Prenat Diagn 2019;39:1162-5.
14. Przbyl J, Spans DA, Lum DA, Zhu S, Vennam S, Forgo E, et al. Detection of circulating tumor DNA in patient with uterine leiomyomas. JCO Precision Oncology

2019;3:1-9.
15. Dharajiya NG, Namba A, Horiuchi I, Miyai S, Farkas DH, Almasri E, et al. Uterine leiomyoma confounding a noninvasive prenatal test result. Prenat Diagn 2015;35:990-3.
16. Bunnell ME, Wilkins-Haug L, Reiss R. Should embryos with autosomal monosomy by preimplantation genetic testing for aneuploidy be transferred?: Implications for embryo selection from a systematic literature review of autosomal monosomy survivors. Prenat Diagn 2017;37:1273-80.
17. Rein MS, Friedman AJ, Barbieri RL, Pavelka K, Fletcher JA, Morton CC. Cytogenetic abnormalities in uterine leiomyomata. Obstet Gynecol 1991;77:923-6.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 82-90

OBSTETRICS

Accuracy of 12-hour versus 24-hour Urine Collection for Diagnosis of Preeclampsia

Sasipimon Sarnnok, M.D.*,
Siraya Kitiyodom, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand*

ABSTRACT

Objectives: To evaluate the accuracy of a 12-hour urine collection compared to a 24-hour urine collection for diagnosis of preeclampsia.

Materials and Methods: The diagnostic study was conducted between March and September 2020 at Maharat Nakhon Ratchasima Hospital, Thailand. The participants were pregnant women at ≥ 20 weeks of gestation composed with blood pressure ≥ 140/90 mmHg or clinically suspected preeclampsia. The participants were hospitalized for evaluation of blood and urine protein analysis. The 24-hour urine protein collection was stratified to the two 12-hour urine protein collection samples. The statistical analyses were used to analyze the accuracy of the test and determine the appropriate cut-off value of 12-hour urine protein compared with the gold standard of the 24-hour urine protein value.

Results: The study included 87 participants with 12-hour urine collection, which comprised 174 samples to compare with 24-hour urine collection. The incidence of preeclampsia was 47 patients (54%). The 12-hour urine collection included 174 samples. The appropriate cut-off value was ≥ 143 mg with sensitivity of 89.8%, specificity of 90.8%, and accuracy of 90.2% with near-perfect agreement (Cohen's kappa 0.82). The 12-hour urine collection test offered higher accuracy than urine protein creatinine ratio and urine protein dipstick test.

Conclusion: The 12-hour urine collection provided high accuracy results and was the alternative test to diagnose preeclampsia.

Keywords: preeclampsia, proteinuria, 24-hour urine protein.

Correspondence to: *Sasipimon Sarnnok, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand. E-mail: giftsasipimon @gmail.com*

Received: 29 September 2020, **Revised:** 11 November 2020, **Accepted:** 29 December 2020

ความแม่นยำในการใช้ปริมาณโปรตีนในปัสสาวะ 12 ชั่วโมงเทียบกับปริมาณโปรตีนในปัสสาวะ 24 ชั่วโมงในการวินิจฉัยครรภ์เป็นพิษ

ศศิพิมล สารนอก, สิรยา กิติโยดม

บทคัดย่อ

วัตถุประสงค์: *ศึกษาความแม่นยำในการใช้โปรตีนในปัสสาวะ 12 ชั่วโมง วินิจฉัยครรภ์เป็นพิษ*

วัสดุและวิธีการ: *การวิจัยเชิงวินิจฉัยในโรงพยาบาลมหาราชนครราชสีมา ระหว่างมีนาคม-กันยายน พ.ศ.2563 ในสตรีตั้งครรภ์ที่อายุครรภ์ตั้งแต่ 20 สัปดาห์ ร่วมกับความดันโลหิตสูง ≥ 140/90 mmHg หรือมีอาการสงสัยภาวะครรภ์เป็นพิษ ผู้เข้าร่วมงานวิจัยได้ถูกรับไว้ในโรงพยาบาล เพื่อเจาะเลือดและเก็บปริมาณปัสสาวะ 24 ชั่วโมง แบ่งเป็น 2 ช่วง ผู้เข้าร่วมวิจัยหนึ่งรายจะเก็บปริมาณโปรตีนในปัสสาวะ 12 ชั่วโมง 2 ตัวอย่าง เพื่อนำไปเทียบกับการวินิจฉัยด้วยโปรตีนในปัสสาวะ 24 ชั่วโมง และนำข้อมูลวิเคราะห์เพื่อหาเกณฑ์ปริมาณโปรตีนที่เหมาะสมและมีความแม่นยำในการวินิจฉัยครรภ์เป็นพิษสำหรับการเก็บปัสสาวะ 12 ชั่วโมง*

ผลการศึกษา: *จากกลุ่มตัวอย่าง 87 คน มีโปรตีนในปัสสาวะ 12 ชั่วโมงจำนวน 174 ตัวอย่าง พบว่ามีภาวะครรภ์เป็นพิษ 47 คน (ร้อยละ 54) และเกณฑ์วินิจฉัยครรภ์เป็นพิษที่เหมาะสมสำหรับการเก็บโปรตีนในปัสสาวะ 12 ชั่วโมงคือ 143 มิลลิกรัม ความแม่นยำร้อยละ 90.2, ความจำเพาะร้อยละ 90.8, ความไวร้อยละ 89.8 และ Cohen k 0.802 (Near prefect agreement) โดยแม่นยำมากกว่า urine protein creatinine ratio และ Urine protein dipstick*

สรุป: *ปริมาณโปรตีนในปัสสาวะ 12 ชั่วโมงมีความแม่นยำค่อนข้างสูง สามารถใช้เป็นทางเลือกหนึ่งในการใช้วินิจฉัยครรภ์เป็นพิษ*

คำสำคัญ: *ครรภ์เป็นพิษ, โปรตีนในปัสสาวะ, ปริมาณโปรตีนในปัสสาวะ 24 ชั่วโมง*

Introduction

Hypertensive disorder in pregnancy is a common disorder and leading cause of maternal and perinatal mortality. In particular, preeclampsia is the most dangerous and complicated condition which is detected approximately 2-8% of all pregnancy and 16% of maternal death worldwide.1 Hypertensive disorder in pregnancy is diagnosed when systolic blood pressure is elevated ≥ 140 mmHg and/or diastolic blood pressure above 90 mmHg and occurs after 20 weeks of gestation[1,2]. Proteinuria remains an important diagnostic criterion for preeclampsia, which differs from other maternal hypertensive disorders[3].

Proteinuria is defined by a few methods, including a 24-hour urine protein collection, or urine protein creatinine ratio (UPCR), or urine protein dipstick test. However, 24-hour urine protein collection is the gold standard to diagnose proteinuria, which is defined as ≥ 300mg/dL without others causes[3,4]. The difficulty of a 24-hr urine collection includes time consuming and required hospital stay. This study aimed to find the method to reduce time of urine protein collection while providing high sensitivity and specificity for the diagnosis of preeclampsia.

According to the prospective observational study conducted by Siva et al[5], a 12-hour urine collection with a 150 mg cut-off values for proteinuria was performed among pregnant women after 20 weeks of gestation with hypertension and suspected preeclampsia. The study illustrated that 42% of samples diagnosed with preeclampsia and the specificity of test reached 91.7% with a sensitivity of 85.9% and no significant difference was found between the time of collection[5].

The aim of this study was to test the hypothesis that a 12-hour urine collection could be used as the gold standard instead of a 24-hour urine collection for diagnosis of preeclampsia.

Materials and Methods

The study was conducted between March and September 2020 at Maharat Nakhon Ratchasima Hospital, Thailand, after approval by the Committee on Human Right Relate to Research Involving Human Subjects. The study included participants who were pregnant women at 20 or more weeks of gestation with high blood pressure, defined by systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or clinically suspected preeclampsia conditions including headache, epigastric pain, blurred vision, excessive weight gain, leg edema, or abnormal presence of protein in urine[4,6]. The exclusion criteria limited the factors affecting abnormal urine protein such as previously identified nephropathy, abnormal vaginal discharge, or urinary tract bleeding. The sample size was determined from the following formula to estimate an infinite population proportion. According to Silva et al[5], the equation was derived and substituted with the following values: d=15% of sensitivity at 95% significance level, sensitivity of 12-hour urine collection = 0.85 and prevalence of preeclampsia was 0.42[5]. As a result, the calculated sample size was ≥ 79.

After the informed consents were collected, the participants were admitted to observe their blood pressure levels, routine blood and urine examination (urine protein dipstick, UPCR, and 24-hour urine collection) for diagnosis of preeclampsia. Blood pressure measurement was regularly performed every 4 hours or earlier in those with extremely high blood pressure. The clinically severe feature of preeclampsia was observed.

A 24-hour urine collection period was divided into 2 periods of 12-hour urine collection, using 2 containers for collection. The collection time was divided into the two periods because it aimed to examine whether urine protein values of both periods were correlated for diagnosis of preeclampsia. The time to collection was labeled properly on both containers to avoid confusion during collection and laboratory test.

In this study, the participants must void completely before the collection and urine samples were sent for analysis and UPCR according to the

standard protocol and they were required to void before the collection and to urinate for the final collection to ensure that the samples were collected accurately for 12-hour collection.

Urine samples were sent to laboratory, where the two containers were measured the amount of protein in urine separately. Urine protein values were reported in accordance with the time of collection. The urine samples from both containers were combined to generate a 24-hour urine collection sample and used to analyze 24-hour urine protein values. Finally, the two values of 12-hour urine protein were compared with the 24-hour urine protein levels (2:1 ratio). Moreover, reliability of the findings of 12-hour and 24-hour urine collection were considered by comparing amount of creatinine secretion in terms of lean body mass (in kg). The creatinine secretions in the participants were approximately 15-20 mg/kg[7].

The mean blood pressure values during hospitalization were analyzed. A 12-hour urine protein, 24-hour urine protein, UPCR and urine protein dipstick were collected. The final diagnosis was confirmed after 24-hour urine collection. All participated pregnant women were monitored closely during pregnancy until labor to detect their pregnancy outcomes and observed the incidence of preeclampsia.

The data were analyzed using STATA/IC software version 12.0. The continuous data were expressed to assess normal distribution. The Cohen's kappa test was used to assess the reliability of a 12-hour collection method compared with a 24-hour collection method. To evaluate the validity of the 12-hour test, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and correlation of the two periods of urine collection times were calculated[8].

Results

A total of 92 eligible pregnant women were recruited. Five women were excluded from the study: one participant refused to treatment, two participants diagnosed with chronic hypertension with proteinuria, and two participants diagnosed with nephrotic or nephritis syndrome (Fig. 1).

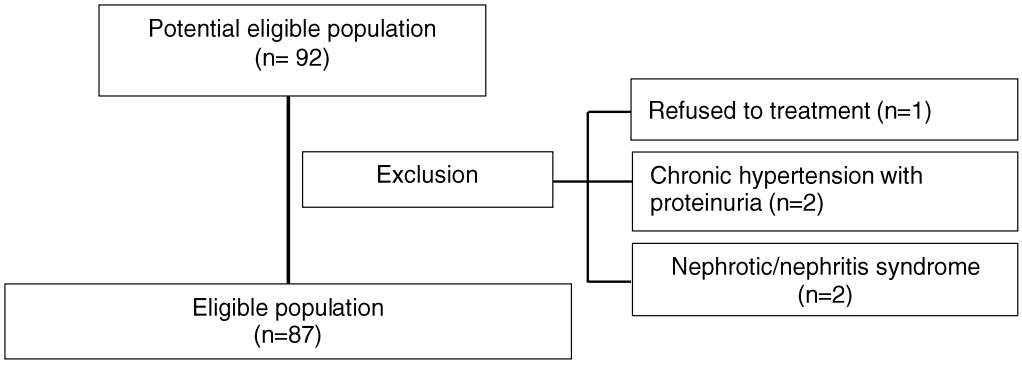


Fig. 1. Flow diagram for the study population.

The remaining 87 women were included in the study. The 12-hour urine collection included 174 samples compared with 24-hour urine collection (ratio 2:1). In which 47 women were diagnosed with preeclampsia (54%). The baseline characteristics of participants were illustrated in Table 1.

As shown in Table 1, participated pregnant women were between the ages of 17-43 years with the mean age of 31 years old and 52.9% of them were obesity (pre-pregnancy body mass index (BMI) ≥ 27 kg/m^2). The prevalence of underlying disease of overt diabetic mellitus and chronic hypertension was found equally at 23% and 8% of patients had both diseases. The rate of women with history of previous pregnancy

with preeclampsia was 8%. After the confirmation of 24-hour urine protein collection for diagnosis preeclampsia, the incidence of preeclampsia and chronic hypertension with superimpose preeclampsia were 47 participants (54%). After pregnancy follow-up, 6 participants (15%) diagnosed with gestational hypertension or chronic hypertensions (without abnormal proteinuria) were categorized as preeclampsia. The study found that the mean gestational age at delivery was 36 weeks, term delivery was 64.4%, and preterm birth was 34.5%. One woman was diagnosed with chronic hypertension with superimposed preeclampsia at 20 weeks of gestation and terminated the pregnancy.

Table 1. Characteristics of the participants (n = 87).

Characteristics	Mean	Median (min-max)
Age, years	30.9 ± 6.11	31 (17-43)
Parity		
Nulliparity	29 (33.3%)	
Multiparity	58 (66.7%)	
Gestational age (GA), weeks	33.7 ± 4.36	35 (20-40)
Singleton pregnancy	85 (97.7%)	
Twin pregnancy	2 (2.3%)	
Body mass index (BMI), kg/m^2		
Pre-pregnancy	27.4 (17.5-49.9)	
During admission	32.7 (20.0-56.4)	
History preeclampsia previous pregnancy	7 (8%)	
Underlying disease		
Overt diabetic mellitus (DM)	20 (23%)	
Chronic hypertension (CHT)	20 (23%)	
Both CHT and DM	8 (9.2%)	
Systemic lupus erythematosus	1 (1.1%)	
Obesity, BMI ≥ 27kg/m^2	46 (52.9%)	
Blood pressure during admission, mmHg		
Mean SBP	144.4 ± 12.97	140 (120-190)
Mean DBP	92.31 ± 9.13	90 (75-120)
Diagnosis		
Gestational Hypertension (GHT)	24 (27.5%)	
Preeclampsia	39 (44.8%)	
Chronic hypertension (CHT)	13 (14.9%)	
CHT with superimpose preeclampsia	8 (9.2%)	
Not pregnancy induced hypertension*	3 (3.6%)	
Preeclampsia after diagnose GHT/CHT	6 (15%)	
GA at delivery, weeks	36.25 ± 3.17	37 (21-40)
Abortion	1 (1.1%)	
Preterm	30 (34.5%)	
Term	56 (64.4%)	

* Not meet eligibility criteria of pregnancy induced hypertension or chronic hypertension

As shown in Table 2, the median represented the findings in this study because the data were not normally distributed. The median 24-hour urine protein was 310 mg and the medians of 12-hour urine protein between the first and the second collection of proteinuria were 151 and 155 mg, respectively.

The receiver operating characteristic (ROC) curve was employed for the analysis of all 174 samples for 12-hour urine protein collection. The purpose was to identify the sensitivity and specificity of 12-hour urine protein method for diagnosis of preeclampsia compared with 24-hour urine protein method. The area under ROC curve was 0.964 (95% confidence interval (CI) 0.942-0.986). (Fig. 2)

Table 2. Urine protein values.

Urine protein values	Median (min-max)
24-hour urine collection (mg)	310 (79.2-12974)
12-hour urine collection (mg)	
The first period of proteinuria	151 (14.5-7906)
The second period of proteinuria	155 (11.6-4191)

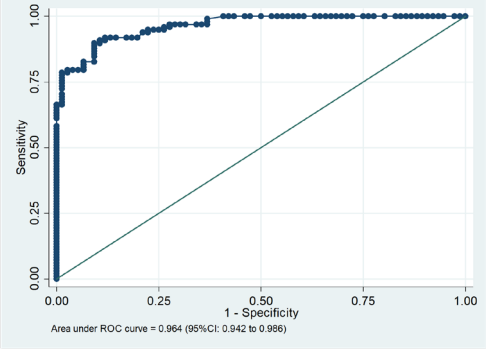


Fig. 2. Sensitivity and specificity of 12-hour urine protein for diagnosis of preeclampsia.

The results appeared that the 12-hour urine protein collection obtained high sensitivity and specificity compared with 24-hour urine protein collection for diagnosis of preeclampsia. The optimal cut-off value of 12-hour urine protein obtained in this study was ≥ 143 mg. This cut-off value presented the highest accuracy of 90.2% and provided a high sensitivity of 89.8%, specificity of 90.8%, PPV of 92.6%, and NPV of 87.3%. Given the cut-off point of ≥ 150 mg as indicated in the study of Silva et al[5] and colleagues, the sensitivity of 85.7% with 90.8% specificity, 92.3% PPV, 83.1% NPV, and 87.9% accuracy were presented in this study.

In addition, Tun et al[9] and Vinayachandran and Darsana[10] suggested the high cut-off value of 12-hour urine protein at ≥ 165 mg, of which it provided high specificity of 100%[9] and 94.7%[10], respectively. The findings from this study were consistent with the previous studies[9,10] (78.6% sensitivity, 97.4% specificity, 97.5% PPV, 77.9% NPV, and 86.8% accuracy). The cut-off value of 12-hour urine protein at ≥ 165 mg illustrated high specificity and PPV, but declined in sensitivity, NPV, and accuracy in comparison to those presented in the cut-off values of 143 and 150 mg.

It was concluded that the cut-off value of 12-hour urine protein of ≥ 143 mg was more appropriate and optimal cut-off to offer higher sensitivity, unchanged

specificity, accuracy with Cohen' kappa value 0.802 (Near perfect agreement) (Table 3).

In addition, this study further assessed the accuracy of the other tests used to verify proteinuria, including UPCR and urine protein dipstick. As illustrated in Table 3, the UPCR test provided 78.8% accuracy, 73% sensitivity, 86% specificity, 87.8% PPV and 70.5% NPV with Cohen' kappa value 0.579 (Moderate agreement). The urine protein dipstick test had the lowest accuracy approximately 67.8% accuracy, 59.2% sensitivity, 78.9% specificity, 78.4% PPV and 60% NPV with Cohen's kappa value 0.368 (Fair agreement). It is illustrated that the 12-hour urine collection test was the best diagnostic test for preeclampsia rather than UPCR and urine protein dipstick test because of high accuracy, specificity, sensitivity, and yielding substantial-near perfect agreement.

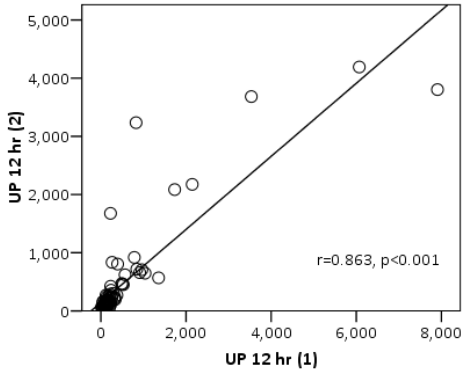
Overall, it would appear that the present findings reasonably confirm that the 12-hour urine protein collection provided acceptable accuracy for diagnosis of preeclampsia.

The sensitivity and specificity of 12-hour urine protein by duration were explained by the ROC curve area. The area under the ROC curve of 12-hour urine protein between the first period and the second period of urine collection were 0.964 (95%CI 0.931-0.966) and 0.967 (95%CI 0.938-0.996), respectively and there was no statistically significant difference (p = 0.8726)

Table 3. Reliability and validity of 12-hour urine protein, UPCR, and urine protein dipstick test compared with 24-hour urine protein for diagnosis of preeclampsia.

Cut-off point	Cohen k	p value	Sens (95%CI)	Spec (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
12-hour urine collection							
≥ 143	0.802 (0.713 - 0.891)	< 0.001	89.8 (82 - 95)	90.8 (81.9 - 96.2)	92.6 (85.4 - 97)	87.3 (78 - 93.8)	90.2 (84.8 - 94.2)
≥ 150	0.757 (0.660 - 0.854)	< 0.001	85.7 (77.2 - 92)	90.8 (81.9 - 96.2)	92.3 (84.8 - 96.9)	83.1 (73.3 - 90.5)	87.9 (82.1 - 92.4)
UPCR							
≥ 0.3	0.579 (0.409 - 0.749)	< 0.001	73.5 (58.9 - 85.1)	86.1 (70.5 - 95.3)	87.8 (73.8 - 95.9)	70.5 (54.8 - 83.2)	78.8 (68.6 – 86.9)
Urine protein dipstick							
≥ 1^{+}	0.368 (0.182-0.555)	0.001	59.2 (44.2-73)	78.9 (62.7-90.4)	78.4 (61.8-90.2)	60 (45.2-73.6)	67.8 (56.9-77.4)

Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval, UPCR: urine protein creatinine ratio



Abbreviation:
UP12hr(1) = The first period of urine collection,
UP12hr(2) = The second period of urine collection,
r = Pearson correlation coefficient

Fig. 3. Correlation of timed urine collection between two periods.

The study found that time to collection of 12-hour urine was correlated with the diagnosis of preeclampsia. The reliability identified by interclass correlation coefficient (ICC) was 0.902 (95%CI 0.850-0.9360) and Pearson correlation was 0.863 ($p < 0.001$). (Fig. 3)

Discussion

Preeclampsia is the syndrome of a new-onset character of high blood pressure with proteinuria after 20 weeks of gestational age. At present, diagnosis of preeclampsia without proteinuria is acceptable when the presence of extremely high blood pressure measurement at ≥ 160/100 mmHg or clinically severe feature of preeclampsia conditions; including headache, abnormal vision, epigastrium pain, pulmonary edema, or abnormal laboratory consisting of low platelets, hemolysis, elevate liver enzyme, creatinine, or coagulopathy[9].

However, pregnant women with high blood pressure without extremely high blood pressure or absent clinically severe feature form of preeclampsia, the 24-hour urine protein collection is the gold standard test to verify proteinuria[10]. Even if, the UPCR and urine protein dipstick methods provide low accuracy, the tests could be used as a rapid test for diagnosis of preeclampsia and immediate optimal management.

Two-thirds of the participants were multiparity which differ from the previous knowledge, in which nulliparity increased the risk of preeclampsia. The data were analyzed and found that the multiparous participants in this study were significantly associated with high maternal age which increased to 41.4% ($p = 0.024$) and were not associated with overt diabetes, chronic hypertension, or obesity. Both nulliparous and multiparous participants did not represent the risk of pregnancy hypertension in this study.

The mean blood pressure values during admission included the SBP of 144.4 mmHg (120-190 mmHg) and the DBP of 92.3 mmHg (75-120 mmHg). Most participants who had high blood pressure were included in the study, except for the 3 participants with normal blood pressure consistently. They were included because of the presence of signs and symptoms of preeclampsia; however, their final diagnoses were not eligible for diagnosed pregnancy-induced hypertension and remained in the analysis.

This study stratified the 24-hour urine collection to two periods of collection, using 2 samples of 12-hour urine collection and compared with 24-hour urine protein as a ratio (2:1). The findings revealed that the appropriate cut-off value of 12-hour urine protein was at ≥ 143 mg, yielding the highest accuracy up to 90.2% with reliability indicated by the Cohen's kappa value of 0.802 (Near perfect agreement). Apparently, the findings provided evidence that the accuracy of cut-off value at ≥ 143 mg was higher than the cut-off value at ≥ 150 mg, presented in previous study conducted by Silva et al[5], where the accuracy was 87.9% with the Cohen's kappa value of 0.757 (substantial agreement interpretation).

The study showed that the proper cut-off value at ≥ 143 mg was lower than the cut-off value presented in the previous study. These findings suggested the knowledge to early diagnosis of preeclampsia or consideration of preeclampsia in a case when urine protein value was below 150 mg and the cut-off value ≥ 150 mg of 12-hour urine collection was used.

The 12-hour urine collection test was the best diagnostic test for preeclampsia rather than UPCR and urine protein dipstick test because of high accuracy, specificity, sensitivity, and yielding substantial-near perfect agreement.

Time to collection of 12-hour urine protein was correlated with the diagnosis of preeclampsia. The correlation between the two periods of collection were explained by Pearson correlation coefficient of 0.863 ($p <0.001$) and ICC = 0.902 (95%CI 0.850-0.936).

The strength of study had several. First, it was the prospective diagnostic study. Second, the findings were examined from urine protein values and other laboratory test results which deliver unbiased results. The limitation of the study was small sample size used in the analysis which could affect reliability.

Conclusions

In conclusion, the 12-hour urine protein collection offered the acceptable accuracy compared with the gold standard of 24-hour urine collection for diagnosis of

preeclampsia. The appropriate cut-off value of 12-hour of urine protein for diagnosis of preeclampsia in this study was ≥ 143 mg with 90.2% accuracy.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:e1-25
2. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management: NICE Guideline [NG133] 2019. Available from: https://www.nice.org.uk/guidance/ng133/resources/hypertension-in-pregnancy-diagnosis-and-management-pdf-66141717671365 [Accessed January 9, 2020].
3. Cunningham FG, Leveno KJ, Bloom SL, Spong C, Dashe JS. Hoffman BL, et al. Williams obstetrics. 25th ed. New York: McGraw-Hill education medical 2018;1344.
4. Lim KH, Steinberg G. Preeclampsia: practical essentials, overview, pathophysiology [Internet]. Emedicine. medscape.com2018 [updated 2018 November 29; cited 2020 Jan 9]. Available from: https://emedicine.medscape.com/article/1476919-overview.
5. Silva RM, Pereira SR, Rego S, Clode N. Accuracy of 12-hour urine collection in the diagnosis of pre-eclampsia. Int J Gynecol Obstet 2018;142:277-82.
6. Leeman L, Dresang ML, Fontaine WP. Hypertensive disorders of pregnancy. Am Fam Physician 2016;93: 121-9.
7. Thomas B. Proteinuria workup: approach considerations, renal biopsy [Internet]. Emedicine.medscape.com 2020 [updated 2020 Mar 25; cited 2020 Nov 30]. Available form: https://emedicine.medscape.com/article/238158-overview
8. Watson PF, Petrie A, Method agreement analysis: a review of correct methodology. Theriogenology 2010;73:1167-79.
9. Tun C, Quiñones JN, Kurt A, Smulian JC, Rochon M. Comparison of 12-hour urine protein and protein:creatinine ratio with 24-hour urine protein for the diagnosis of preeclampsia. Am J Obstet Gynecol 2012;207:233.e1-8.
10. Vinayachandran S, Darsana K. Correlation of spot urine albumin and 12-hour urine protein with 24-hour urine protein in pre-eclampsia. J Evid Based Med Health 2017;4:5486-90.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 91-99

GYNAECOLOGY

Comparing the Efficacy in Reducing Pelvic Pain Score at 3 Months after Treatment in Clinically Diagnosed Endometriotic Patients between Leuprolide Acetate and Depot Medroxyprogesterone Acetate: A randomized controlled trial

Akrapat Sowannakul, M.D.*,
Patcharin Kiettisanpipop, M.D.*,
Kittipong Kongsomboon, M.D.**

** Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok, Thailand*
*** Department of Preventive and Social medicine, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok, Thailand*

ABSTRACT

Objectives: To compare the efficacy of 11.25 mg-leuprolide acetate (Enantone L.P.) and 150 mg-intramuscular depot medroxyprogesterone acetate (DMPA-IM) (Depo-Progesta) in the reduction of pelvic pain score, satisfaction of the patients after 3 months of treatment and associated side effects.

Materials and Methods: The study design was based on a randomized controlled trial, which was conducted in thirty-six patients who attended gynecologic outpatient department at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Centre (MSMC). These patients were randomized into two groups, either the 11.25 mg-leuprolide acetate or the DMPA-IM group at their first visit. The pelvic pain scores were gathered by using the numerical rating scale at their first visit and 3 months after treatment. The satisfaction score was gathered by using rating scale 1-10. Side effects were collected data as yes or no. Mann-Whitney U test was used to evaluate both the efficacy through the improvements in pelvic pain score and patient's satisfaction score. Finally, Chi-square test was used to evaluate side effects of both medications.

Results: The efficacy to reduce the pelvic pain score was similar between the 11.25 mg- leuprolide acetate and DMPA-IM group after 3 months of treatment. After the treatment, pain score was reduced from 7.00 (6.00, 8.00) [median (interquartile range)] to 2.00 (0.00, 2.00) in leuprolide acetate group and from 8.50 (6.00, 10.00) to 2.00 (2.00, 3.00) in the DMPA-IM group. The median (interquartile range) reduction in pain score was 73.21% (55.56, 100.00) in leuprolide acetate group and 71.43% (60.00, 80.00) in DMPA-IM group. However, this reduction did not show statistical significance between groups. Concerning the secondary objectives of this study, the median (interquartile range) of satisfaction score was 9.00 (7.00, 10.00) in leuprolide acetate group and 8.00 (8.00, 9.00) in DMPA-IM group at 3 months after treatment which were considered high but were not statistically significant between groups. In this study hot flashes were more commonly experienced by the patients in the leuprolide acetate group with statistical significance. In contrast, vaginal spotting was more common in patients of the DMPA-IM group.

Other side effects such as night sweat, mood swing and vaginal dryness experienced by these patients were not statistically different between groups.

Conclusion: This double-blinded randomized controlled trial demonstrated that 11.25 mg-Leuprolide acetate was as effective as 150 mg-DMPA-IM in terms of reduction in endometriosis-related pain and patient satisfaction at 3 months after the initial treatment without significant differences.

Keywords: leuprolide acetate, depot medroxyprogesterone acetate, endometriosis.

Correspondence to: *Patcharin Kiettisanpipop, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok 26120, Thailand. E-mail: patch_arin @hotmail.com*

Received: 30 September 2020, **Revised:** 28 December 2020, **Accepted:** 29 December 2020

การเปรียบเทียบประสิทธิภาพการลดอาการปวดในผู้ป่วยโรคเยื่อบุโพรงมดลูกเจริญผิดที่ ที่ 3 เดือนหลังการใช้ยา Leuprolide acetate และ Depot medroxyprogesterone acetate

อัครพัฒน์ โสวรรณกุล, พัชรินทร์ เกียรติสารพิภพ, กิตติพงษ์ คงสมบูรณ์

บทคัดย่อ

วัตถุประสงค์*: เพื่อเปรียบเทียบประสิทธิภาพในการลดอาการปวดจากโรคเยื่อบุโพรงมดลูกเจริญผิดที่ ที่ 3 เดือนหลังการรักษา และเพื่อเปรียบเทียบผลข้างเคียงที่เกิดขึ้นระหว่างการใช้ยาและความพึงพอใจของผู้ป่วยหลังได้รับการรักษาโรคเยื่อบุโพรงมดลูกเจริญผิดที่ด้วยยา Leuprolide acetate 11.25 mg (Enantone L.P.) และยา Depot medroxyprogesterone acetate 150 mg (Depo-Progesta)*

วัสดุและวิธีการ*: เป็นการศึกษาแบบ double blind prospective randomized controlled trial โดยเก็บข้อมูลจากผู้ป่วย 36 คน ที่มารับการรักษาที่คลินิกนรีเวช โรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี โดยผู้ป่วยจะได้รับการสุ่มแบ่งออกเป็นสองกลุ่ม โดยกลุ่มที่หนึ่งจะได้รับยา Leuprolide acetate 11.25 mg (Enantone L.P.) และกลุ่มที่สอง Depot medroxyprogesterone acetate 150 mg (Depo- Progesta) คะแนนความปวดบริเวณท้องน้อยจะถูกบันทึกโดยใช้ Numerical rating scale ก่อนการรักษาและที่สามเดือนหลังการรักษา คะแนนความพึงพอใจใช้ rating scale 1-10 และผลข้างเคียงที่เกิดขึ้นเก็บข้อมูลเป็นใช่และไม่ใช่ จากนั้นนำข้อมูลคะแนนความปวดและความพึงพอใจมาคำนวนทางสถิติมาคำนวณทางสถิติเพื่อเปรียบเทียบหาประสิทธิภาพโดยใช้ Man-whitney U test และผลข้างเคียงที่เกิดขึ้นระหว่างการใช้ยา ใช้ Chi-square test*

ผลการศึกษา*: ประสิทธิภาพในการลดอาการปวดในผู้ป่วยสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ โดยในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) มีค่ามัธยฐาน (ค่าพิสัยระหว่างควอไทล์) ของคะแนนความปวดลดลงจาก*

7.00 (6.00, 8.00) เป็น 2.00 (0.00, 2.00) โดยคิดเป็น 73.21% (55.56, 100.00) และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo- Progesta) คะแนนความปวดลดลงจาก 8.50 (6.00, 10.00) เป็น 2.00 (2.00, 3.00) โดยคิดเป็น 71.43% (60.00, 80.00) และคะแนนความพึงพอใจที่ 3 เดือนหลังการรักษา ในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) มีค่ามัธยฐาน (ค่าพิสัยระหว่างควอไทล์) ของคะแนน 9.00 (7.00, 10.00) และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta) มีคะแนน 8.00 (8.00, 9.00) ซึ่งมีคะแนนจัดอยู่ในระดับสูงทั้งสองกลุ่ม และไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในเรื่องผลข้างเคียงจากการใช้ยาพบว่าในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) พบอาการร้อนวูบวาบมากกว่าอย่างมีนัยสำคัญทางสถิติ และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta) พบเลือดออกกะปริดกะปรอยทางช่องคลอดมากกว่าอย่างมีนัยสำคัญทางสถิติ โดยผลข้างเคียงอื่นๆ เช่น เหงื่อออกกลางคืน, อารมณ์แปรปรวน และช่องคลอดแห้ง ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

***สรุป**: ประสิทธิภาพในการลดอาการปวดท้องน้อยหลังการใช้ยา Leuprolide acetate 11.25 mg (Enantone L.P.) และยา Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta)ที่สามเดือนหลังเริ่มต้นการรักษา ในผู้ป่วยโรคเยื่อบุโพรงมดลูกเจริญผิดที่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

***คำสำคัญ**: ยา Leuprolide acetate, ยา Depot medroxyprogesterone acetate, เยื่อบุโพรงมดลูกเจริญผิดที่*

Introduction

Endometriosis is one of the most common and troublesome gynecological diseases experienced by females of reproductive age. It is generally known as a chronic condition in which the endometrial tissue grows outside the endometrial cavity. The tissue usually seeds within the pelvic cavity, such as pelvic viscera, pelvic organs and the peritoneum[1,2]. Extra-pelvic endometriosis is less common; however, it could present in the lungs, brain, and gastrointestinal tract[2]. Symptoms commonly found in patients include dysmenorrhea, pelvic pain and infertility. The incidence is approximately 70-90% of those who are presented with pelvic pain[3]. However, the clinical presentation is quite inconsistent, with some patients experiencing severe symptoms while the others have little to no symptom. Generally, endometriosis could be diagnosed clinically in patients presenting with progressive dysmenorrhea, chronic pelvic pain, dyspareunia and infertility[4-6]. Many institutes advocate treatment of patients who are clinically diagnosed in order to decrease the percentage of those with subsequent complications[7]. Apart from those with surgical indication or those with fertility desire, the mainstay of treatment is medical intervention. There is no evidence as to which regimen is the most superior. Treatment is often personalized by patient's compliance and response to treatment, drug tolerance, and financial status. Examples of hormonal treatment are progestogen, anti-progestogen and gonadotropin releasing hormone agonist (GnRH agonist)[7, 8].

Progestogen has anti-endometriotic effects. It triggers endometrial decidualization which consequently leads to gradual endometrial thinning. However, its downside may be vaginal spotting, weight gain and delayed return of ovulatory function[1,2,7,9]. GnRH agonist, on the other hand, provides non-pulsatile stimulation to the hypothalamus, and thereby decreases estrogen level through inhibiting luteinizing hormones and follicle stimulating hormones production[1,2,10,11]. Furthermore, it can also reduce adhesion formation by decreasing plasminogen activator and matrix metalloproteinase activities[1,12]. Since the inhibition occurs at the top of the hormonal cascade, GnRH induces a state of reversible pseudomenopause which may effectively cause regression of endometriotic lesions. However, patients may experience several symptoms mimicking true menopause with an increased risk of osteoporosis after 6 months use[2].

In most public hospitals in Thailand, the most commonly used medical treatment of endometriosis are depot medroxyprogesterone acetate (DMPA) and leuprolide acetate[13]. Although DMPA appears to be a cost-effective choice, leuprolide acetate or GnRH agonist is believed to have a greater potency in reducing estrogen level and causes better regression of endometriotic lesions due to its efficacy to reduce estrogen level more than DMPA.

The primary objective of this study was to compare the efficacy of 11.25 mg-leuprolide acetate and 150 mg-intramuscular depot medroxyprogesterone acetate (DMPA-IM) in the reduction of pelvic pain score at 3 months after initial treatment. Moreover, the secondary objectives were to compare satisfaction of the patients at 3 months after initial treatment and associated side effects during 3 months of treatment.

Materials and Methods

This study was conducted as a prospective, double-blinded, randomized controlled trial in clinically diagnosed endometriotic patients attending gynecologic out-patient department (OPD) at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) during July 2019 to September 2020. This study was approved by the institute's ethics committee (registration number SWUEC/F-436/2561).

In this study, the sample size was estimated from pilot study that showed mean of pain score after treatment as 1.14 & 2.29 and standard deviation as 2.29 with two-tail test, with an alpha-error of 5%, 90% power and ratio of 1:1. Therefore, the number of participants in study were 18 in each group.

The target population were those presented with pelvic pain or dysmenorrhea without being clinically diagnosed with endometriosis. We included patients with history and physical examination which suggest endometriosis. The inclusion criteria were the presence of clinically diagnosed endometriosis-associated pelvic pain over at least 6 months in females between the age of 18 to 49, which was defined as progressive dysmenorrhea, non-cyclical chronic pelvic pain and deep dyspareunia, with progressive dysmenorrhea as the main chief complaint. To diagnose the patients, clinical examination was done which included inspection of the vagina using a speculum especially at posterior fornix of vaginal wall, bimanual and rectovaginal palpation to search for infiltration or nodules of the vagina, uterosacral ligaments or pouch of Douglas, and detection of any painful induration. Transvaginal ultrasound was used to find the ovarian endometrioma and to rule out other diagnoses such as adenomyosis, myoma uteri or adnexal mass that may cause symptoms mimicking those of endometriosis. The exclusion criteria included pregnancy, continuous use of hormonal therapy and medical diseases including diabetes mellitus, dyslipidemia, venous thrombosis, coronary artery disease, stroke, epilepsy, osteoporosis, chronic liver disease. In addition, those with a history of breast or gynecologic malignancy which could be stimulated by hormone and those with undiagnosed abnormal uterine bleeding were also excluded. More specific to the medications used in this study, patients with a history of hypersensitivity to DMPA or leuprolide acetate (i.e. urticaria, puffy eyelids or respiratory distress), and those that cannot tolerate side effect of the drugs such as hot flashes or vaginal spotting. Finally, those with fulfilled indications for surgical management or cases which pathological tissue was required due to inability to rule out malignancy were excluded as well.

Patients who agreed to participate provided a signed informed consent upon recruitment and were asked to complete a questionnaire evaluating the presence and severity of dysmenorrhea, deep dyspareunia and non-menstrual pelvic pain graded by a score of 0 to 10 using the numerical rating scale (NRS). In addition, information gained from physical examination including pelvic tenderness or induration were also recorded on the questionnaire. Subsequently, these patients underwent simple randomization to either 150 mg-DMPA-IM (Depo-Progesta 150 mg/3mL) or 11.25 mg-leuprolide acetate (Enantone L.P. 11.25mg), both via intramuscular route. Both the researchers and patients were blinded to the randomization. The patients were injected with these medications by a nurse at the gynecologic OPD and sent home after a short duration of observation for immediate side effects.

A follow-up by phone was done at 1 and 2 months after initial treatment and a follow-up visit of the patients included in this study was 3 months after the initial treatment. Severity of pain was reevaluated in the follow-up visit using the NRS. Satisfaction score was recorded as a grade based on a scale of 1 to 10. Finally, the side effects caused by the medications, for example, hot flashed, night sweats, mood swings, vaginal spotting and dryness were categorically recorded as either yes or no.

Thirty-nine patients (n = 39) were initially eligible for participation in which 3 patients were excluded from data analysis due to loss to follow-up, recently diagnosed cervical lesion and subsequently deny participating, and inability to tolerate side effects of leuprolide acetate. Therefore, thirty-six women (n = 36) were included in data analysis. All analyses were done using Stata version 15.1 (StataCorp. Stata statistical software: Release 15.1. College Station, TX: Stata Corporation, Texas, USA, 2017). Normality of data was tested before analysis using Shapiro-Wilk test. Continuous data between the two intervention groups were tested by independent t-test and Mann-Whitney U test for parametric, and non- parametric distribution, respectively. Chi square test or fisher exact test was used to test categorical data. All statistical analyses

were two-tailed, and the significance level of 0.05 was used. 95% confidence interval was calculated.

Results

After corresponding to the inclusion and exclusion criteria shown in Fig. 1, the demographic characteristics of the patients included in this study are shown in Table 1. The mean age was 33.44 ± 5.83 years in leuprolide acetate group and 33.11 ± 1.69 in DMPA-IM group. The median weight and BMI of patients were 56.00 (53.25, 61.60) kilograms and 22.00 (19.86, 24.52) kg/m^2 in leuprolide acetate group and 56.00 (53.25, 61.60) and 22.46 (21.33, 28.47) kg/m^2 in DMPA-IM group. The median scores of chronic pelvic pain and duration of symptoms of leuprolide acetate group were 7.00 (6.00, 8.00) and 12 months (6, 36), while those were 8.50 (6.00, 10.00) and 18 months (12, 36) for the DMPA-IM group. The two groups revealed no significant differences in these baseline characteristics.

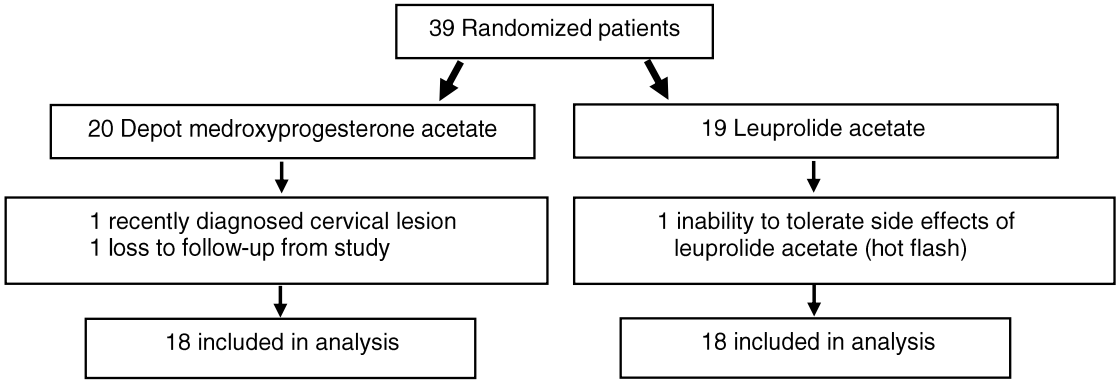


Fig. 1. Profile of patient follow-up following randomization to either depot medroxyprogesterone acetate or leuprolide acetate.

Table 1. Demographic characteristics.

Characteristic	Depot medroxyprogesterone acetate (n = 18)	Leuprolide acetate (n = 18)	p value
Age (year), mean ± SD	33.11±1.69	33.34±5.83	0.880*
Weight (kgs), median (IQR)	56.50 (47.50, 65.50)	56.00 (53.25, 61.60)	0.824**
BMI (kgs/m^2), median (IQR)	22.00 (19.86, 24.52)	22.46 (21.33, 28.47)	0.700**
Pelvic pain score, median (IQR)	8.50 (6.00, 10.00)	7.00 (6.00, 8.00)	0.082**
Duration(months), median (IQR)	18 (12, 36)	12 (6, 36)	0.471**

SD: standard deviation, IQR: interquartile range, BMI: body mass index
*Independent T-Test, ** Mann-Whitney U test

Pelvic pain scores after the initial treatment in both groups are shown in Table 2. After the treatment, pain score was reduced from 7.00 (6.00, 8.00) to 2.00 (0.00, 2.00) in leuprolide acetate group and from 8.50 (6.00, 10.00) to 2.00 (2.00, 3.00) in the DMPA-IM group at 3 months after treatment. Therefore, the pain score was significantly reduced from baseline in both groups. but were not different in terms of statistical significance between them.

Concerning the secondary objectives of this study, the satisfaction score was 9.00 (7.00, 10.00) in leuprolide acetate group and 8.00 (8.00, 9.00) in DMPA-

IM group at 3 months after treatment, which were not statistically significant between groups.

The associated side effects arising from both medications used during this study are shown in Table 3. Hot flashes were more commonly experienced by the patients in the leuprolide acetate group with statistical significance. In contrast, vaginal spotting was more common in patients of the DMPA-IM group. Other side effects such as night sweat, mood swing and vaginal dryness experienced by these patients were not statistically different between groups.

Table 2. Pelvic pain score after receiving medication.

Pelvic pain score	Depot medroxyprogesterone acetate median (IQR)	Leuprolide acetate median (IQR)	p value*
Baseline pain score	8.50 (6.00, 10.00)	7.00 (6.00, 8.00)	0.082
After 3 months	2.00 (2.00, 3.00)	2.00 (0.00, 2.00)	0.274
% Improvement after 3 months	71.43 (60.00, 80.00)	73.21 (55.56, 100.00)	0.274

IQR: interquartile range
*Mann-Whitney U test

Table 3. Side effect of medication.

Side effect of medication	Depot medroxyprogesterone acetate n (%)	Leuprolide acetate n (%)	p value*
Hot flash	11/18 (61.11)	14/18 (77.78)	0.018
Night sweat	11/18 (61.11)	12/18 (66.67)	0.729
Mood swing	11/18 (61.11)	10/18 (55.56)	0.735
Spotting	16/18 (88.89)	6/18 (33.33)	0.001
Vaginal dryness	7/18 (38.89)	10/18 (55.56)	0.317

*Chi-square test

Discussion

Based on this study, the cohort of population was selected based on the clinical diagnosis of endometriosis and its associated pain, primarily through history taking and physical examination. From the review of literature, the variety of presenting symptoms and its severity is usually not correlated with the type or size of endometriotic lesions found via diagnostic laparoscopy[6,11]. Currently, there are many treatment options of endometriosis including medical and surgical options. Medical treatment is a choice for patients who do not wish for pregnancy and require reduction in endometriosis-related pain. On the other hand, surgical option which is more invasive seems appropriate for patients who have fertility need and require reduction in pain. In this study, we aimed to compare two of the most commonly used medical treatments in practical management. Firstly, leuprolide acetate, its action to inhibit the hypothalamic-pituitary-ovarian axis and subsequent endometrial growth to menopausal-like state makes it an effective choice but its cost may prevent some patients from selecting this option. For DMPA-IM, it is commonly used in clinical practice because of its efficacy in reducing endometriosis-related pain, well-documented safety profile, and cost-effectiveness. The medications chosen in this study are those that are traditionally used to treat endometriosis-associated pain and have established a well-known

safety profile and efficacy comparable with surgical management[7-11].

In general, the medical treatments selected in this study are more cost-effective compared with surgery[13]. In fact, the mechanism of actions of these medications are to suppress endometrial proliferation and therefore are commonly used in the clinical setting of endometriosis[7-11]. Based on previous studies, the utilization of both depot medroxyprogesterone acetate and leuprolide acetate led to good clinical outcomes in terms of reducing endometriosis-related pain. From Crosignani, et al. result and in the same way Schlaff et al found that after administration of subcutaneous depot medroxyprogesterone acetate or leuprolide acetate every 3 months for a total of 6 months could reduce pain score at 6 and 18 months after treatment[14,15].

In this randomized, double-blinded controlled trial, leuprolide acetate was shown to be as effective as DMPA-IM in the reduction of endometriosis-associated pain at the follow-up of 3 months after treatment. Theoretically, endometriosis involves local estrogen production and subsequent activation of estrogen receptors which produces various cytokines such as interleukin (IL)-6, IL-8, tumor necrotic factor (TNF)-alpha[16]. From previous literature, leuprolide acetate acts by inhibiting the HPO axis, while progestins activates the pituitary progesterone receptors creating hypoestrogenic and hyperprogestrogenic systemic environment and possibly amenorrhea. However, recent studies also suggest that progestins act locally by inhibiting cytokines such as IL-6, IL-8 and TNF-alpha which is dependent on the expression of their target receptors in an inflammatory environment[17]. Although these medications work through slightly different mechanisms, their efficacy appears to be similar.

Based on this study, both leuprolide acetate and DMPA-IM led to good patient satisfaction with the score of 8-9 from 10. It is considered to be in high level because of reduction in pain score after treatment and associated side effect that can be tolerated. This finding was consistent with the previous literature from Crogsignani which found that the quality of life was greatly improved by using Endometriosis Health Profile-30 Questionnaire (EHP-30) and Short Form 36 Health Survey (SF-36 scales) as tools of measurement[14]. Patient satisfaction as measured by the scores was not statistically different between the two treatment groups. In terms of side effects, hot flashes were most commonly encountered in the leuprolide acetate group. Unfortunately, there was one participant (1/14, 7.14%) who could not tolerate the side effect and required an add-back hormonal therapy. In contrast, intermenstrual bleeding was more significantly reported in the DMPA-IM group. There was no participant who could not tolerate this side effect. These results were comparable with those found by Schlaff et al, in which the experience of side effects of vaginal dryness, mood swings and night sweats were not statistically different between groups[15]. In general, from the follow-up of patients concerning the side effects from the mediations, most participants could tolerate the side effects which correlated with the good satisfaction scores.

The overall results based on the primary and secondary objectives of this study showed that the efficacy of treatment and patient satisfaction in both arms were not significantly different. However, the side effects experienced by the participants and cost-effectiveness were different between the two groups. Therefore, these factors may guide the patient to select an appropriate treatment option in order to maximize its benefits.

The main strength of this study was the selection of patients who have never received medical or hormonal treatment which could have adversely affected the results. In addition, the double-blinded randomized controlled trial nature of this study enabled the production of clinical results which correlate closely with reality.

There are several limitations of this study. First, the insignificant results in this study may be caused from small sample size. Second, uneven normal distribution of data could make them unrepresentative of general population. Third, exclusion of information on the use of other medications for pain control during the study period could have adverse effects on the results. Fourth, follow-up by telephone call may lead to inaccurate information when compared with face-to-face interview. Last, as the endometriosis is a chronic

disease and requires long term management, this study provided only short-term follow-up.

Conclusions

This double-blinded randomized controlled trial demonstrated that 11.25 mg-Leuprolide acetate was as effective as 150 mg-DMPA-IM in terms of reduction in endometriosis-related pain and patient satisfaction at 3 months after the initial treatment without significant differences.

Acknowledgements

This study was granted by Faculty of Medicine, Srinakharinwirot University. The authors would like to thank you to Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University and Dr.Marut Vanitchanont who assisted in editing the manuscript.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Fritz MA, Speroff L. Endometriosis. In: Fritz MA, Speroff L, editors. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lippincott Williams and Wilkins 2011:1211-48.
2. Vanhie A, D'Hooghe TM. Endometriosis. In Berek JS, Berek DL, editors. Berek & Novak's gynecology. 15th ed. United States of America: Lippincott Williams and Wilkins 2012;279-312.
3. Tanmahasamut P, Noothong S, Sanga-Areekul N, Silprasit K, Dangrat C. Prevalence of endometriosis in women undergoing surgery for benign gynecologic diseases. J Med Assoc Thai 2014;97:147-52.
4. Winkel CA. Evaluation and management of women with endometriosis. Obstet Gynecol 2003;102:397-408
5. Cheewadhanaraks S, Peeyananjarassri K, Dhanaworavibul K, Liabsuetrakul T. Positive predicetive value of clinical diagnosis of endometriosis. J Med Assoc Thai 2004;87:740-4.
6. Taylor HS, Adamson GD, Diamond MP, Goldstein SB, Horne AW, Missmer SA, et al. An evidence-based approach to assessing surgical versus clinical diagnosis of symptomatic endometriosis. Int J Gynecol Obstet 2018;142:131-42.
7. Dunselman GA, Vermuelen N, Becker C, Calhaz-Jorge CT, D'Hooghe B. De Bie O, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400-12.
8. Mahutte NG, Arici A. Medical management of endometriosis-associated pain. Obstet Gynecol Clin North Am 2003;30:133-50.
9. Zhou J, Lei ZW, Lü JQ, Sun J, Xu XW. Conservative surgery combined with depot medroxyprogesterone acetate in treatment of moderate or severe endometriosis. Zhonghua Fu Chan Ke Za Zhi 2005;40:5-8.
10. Suen SH, Chan SCS. A Prospective observational study to evaluate the efficacy and safety profiles of leuprorelin 3 month depot for the treatment of pelvic endometriosis. Hong Kong J Gynaecol Obstet Midwifery 2005;5:2-9
11. Baxter N, Black J, Duffy S. The effect of a gonadotrophin-releasing hormone analogue as first-line management in cyclical pelvic pain. J Obstet Gynaecol 2004;24:64-6.
12. Sharpe-Timms KL, Zimmer RL, Jolliff WJ, Wright JA, Nothnick WB, Curry TE. Gonadotropin-releasing hormone agonist (GnRH-a) therapy alters activity of plasminogen activators, matrix metalloproteinases, and their inhibitors in rat models for adhesion formation and endometriosis: potential GnRH-a–regulated mechanisms reducing adhesion formation. Fertil Steril 1998;69:916-23.
13. Winkel CA. A cost-effective approach to the management of endometriosis. Curr Opin Obstet Gynecol 2000;12:317-20.
14. Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006;21:248-56.
15. Schlaff WD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril 2006;85:314-25.
16. Mori T, Ito F, Koshiba A, Kataoka H, Takaoka O, Okimura H et al. Local estrogen formation and its regulation in endometriosis. Reprod Med Biol 2019;18:305-11.
17. Grandi G, Mueller M, Bersinger N, Papadia A, Nirgianakis K, Cagnacci A et al. Progestin suppressed inflammation and cell viability of tumor necrosis factor-α-stimulated endometriotic stromal cells. Am J Reprod Immunol 2016;76:292-8.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 100-108

OBSTETRICS

Effect of Electric Breast Pump versus Conventional Breastfeeding on Onset of Lactation in Post-cesarean Women: A randomized controlled trial

Siriganlaya Muangban, M.D.,
Rungruedee Jeerasap, M.D.,
Thumwadee Tangsiriwatthana, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To study the time to onset of lactation (OL) when using an electric breast pump compared with conventional breastfeeding in post-cesarean women.

Materials and Methods: Thirty-four post-cesarean women under spinal block were randomized into two groups: the electric breast pump group (i.e. conventional breastfeeding combined with electric breast pump) and the conventional breastfeeding group. The electric breast pump group started using the electric breast pump within 3 hours of operation, 15 min for each pumping session, every 3 hours after breastfeeding until time to OL. The conventional breastfeeding group breastfed on demand at least 8 times in 24 hours. Post-cesarean women recorded time to OL by maternal perception when they had any one signs and/or symptoms of breast fullness, breast tingling, milk leakage.

Results: The time to OL in the electric breast pump group was significantly earlier than in the conventional breastfeeding group (43.8 ± 11.0 hours versus 68.3 ± 19.9 hours, respectively, $p < 0.001$). Maternal nipple pain after immediate use of the electric breast pump and breastfeeding ($p = 0.74$), and length of hospital stay ($p = 0.88$) were not statistically significant between groups.

Conclusion: Post-cesarean women in the electric breast pump group had significantly earlier time to OL compared with women in the conventional breastfeeding group.

Keywords: electric breast pump, conventional breastfeeding, onset of lactation.

Correspondence to: *Siriganlaya Muangban, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. E-mail: Siriganlaya37@gmail.com*

Received: 30 September 2020, **Revised:** 15 December 2020, **Accepted:** 29 December 2020

ผลของการใช้เครื่องปั๊มนมไฟฟ้าเปรียบเทียบกับการให้นมบุตรปกติต่อระยะเวลาที่เริ่มหลั่งน้ำนมเต็มเต้าในสตรีหลังผ่าตัดคลอด: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

สิริกัลยา เมืองบาล, รุ่งฤดี จีระทรัพย์, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *ผลของการใช้เครื่องปั๊มนมไฟฟ้าเปรียบเทียบกับการให้นมบุตรปกติต่อระยะเวลาที่เริ่มหลั่งน้ำนมเต็มเต้าในสตรีหลังผ่าตัดคลอด: การทดลองแบบสุ่มที่มีกลุ่มควบคุม*

วัสดุและวิธีการ: *สตรีตั้งครรภ์ที่ได้รับการผ่าตัดคลอดโดยการระงับความรู้สึกด้วยการฉีดยาชาเข้าช่องไขสันหลัง 34 ราย ได้รับการสุ่มเป็น 2 กลุ่ม คือ กลุ่มที่ใช้เครื่องปั๊มนมไฟฟ้า (การให้นมบุตรปกติร่วมกับการใช้เครื่องปั๊มนมไฟฟ้า) และกลุ่มที่ให้นมบุตรปกติกลุ่มที่ใช้เครื่องปั๊มนมไฟฟ้าจะได้เริ่มใช้เครื่องปั๊มนมไฟฟ้าปั๊มเต้านมภายใน 3 ชั่วโมง หลังผ่าตัดคลอดปั๊มนาน 15 นาทีต่อครั้ง ทุก 3 ชั่วโมง หลังจากให้นมบุตร จนมีอาการหรืออาการแสดงของการเริ่มหลั่งของน้ำนมเต็มเต้ากลุ่มให้นมบุตรปกติให้นมบุตรอย่างน้อย 8 ครั้ง ใน 24 ชั่วโมง สตรีหลังผ่าตัดคลอดทั้ง 2 กลุ่ม บันทึกเวลาเมื่อมีอาการและอาการแสดงอย่างใดอย่างหนึ่งของการเริ่มหลั่งของน้ำนมเต็มเต้าโดยการรับรู้ของมารดาได้แก่ เต้านมคัดตึงเสียวแปลบที่บริเวณเต้านมและมีน้ำนมไหลหยด*

ผลการศึกษา: *กลุ่มที่ใช้เครื่องปั๊มนมไฟฟ้าพบว่ามีระยะเวลาการเริ่มหลั่งของน้ำนมเต็มเต้าเร็วกว่ากลุ่มที่ให้นมบุตรปกติอย่างมีนัยสำคัญทางสถิติ (43.8 ± 11.0 ชั่วโมง และ 68.3 ± 19.9 ชั่วโมง, $p < 0.001$) ระดับความเจ็บที่หัวนม ($p = 0.74$) และระยะเวลาในการนอนโรงพยาบาล ($p = 0.88$) ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ*

สรุป: *สตรีหลังผ่าตัดคลอดในกลุ่มที่ใช้เครื่องปั๊มนมไฟฟ้ามีระยะเวลาการเริ่มหลั่งของน้ำนมเต็มเต้าเร็วกว่ากลุ่มที่ให้นมบุตรปกติอย่างมีนัยสำคัญทางสถิติ*

คำสำคัญ: *เครื่องปั๊มนมไฟฟ้า, การให้นมบุตรปกติ, ระยะเวลาที่เริ่มหลั่งน้ำนมเต็มเต้า*

Introduction

Exclusive breastfeeding can reduce, and has a protective effect on, gastrointestinal infections, respiratory diseases, sepsis, and lowers the incidence of sudden infant death syndrome[1]. A long-term outcome of breastfeeding is higher scores on developmental and intelligence tests[2]. United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) recommend initiating breastfeeding within an hour of delivery and continuing to exclusive breastfeeding until six months of life[3-4]. Mothers who exclusively breastfeed with no prelacteal feeding have earlier onset of lactation because infant suckling induces secretion of lactogenic hormones[5].

Lactogenesis stage II starts copious milk production after delivery usually at day 2-3 postpartum[6]. The gold standard for determining lactogenesis stage II is the measurement of milk transfer, which is tested by weighing the infant before and after each breastfeeding[7]. Such test weighing is impractical for use in the general population because it is disruptive for the infant and has a high cost. The onset of lactation (OL) by maternal perception is an alternative method for detecting OL: the mother senses breast fullness, breast tingling, and milk leakage. This method is practicable indicator of lactogenesis stage II due to its being non-invasive, low cost and useful for public health[7].

Delayed OL (> 72 h) is a public health concern because women with delayed OL can cause fetal hypoglycemia, excessive infant weight loss, lack of maternal confidence and shorter breastfeeding duration compared with women who have earlier OL[8,9]. Previous studies reported the factors affecting delayed OL included diabetes, stress, and cesarean section. Cesarean section resulted in a significantly higher rate of delayed OL compared to vaginal delivery (12.1% versus 3.4%)[9]. This result may be explained by the lower rate of early initiation of breastfeeding within the first 24 h, delayed skin-to-skin contact, mother fatigue, and pain from the operative site making it difficult to hold the baby[10,11].

Slusher et al reported that postpartum women who utilized an electric breast pump had significantly higher milk volume compared with hand expression[12]. Fewtrell et al also found that electric breast pump use increased milk volume in mothers whose infants were delivered before gestational age less than 34 weeks[13]. Zhang et al found that post-cesarean women who used electric breast pump had significantly earlier time to OL by test weighing and higher milk supply compared with conventional breastfeeding[14]. There has, however, been no study about the time to OL by maternal perception in post-cesarean women, comparing between electric breast pump and conventional breastfeeding.

The rate of cesarean section has been increasing in both developed and developing countries[15]. Lactation in women who give birth by cesarean delivery can be delayed. The current study was conducted to evaluate the effectiveness of the electric breast pump versus conventional breastfeeding regarding time to OL by maternal perception in post-cesarean women, comparing between electric breast pump and conventional breastfeeding.

Materials and Methods

This randomized controlled trial was approved by the Khon Kaen Hospital Institute Review Board in Human Research (KEF62019) before the study. We included term singleton post-cesarean women under spinal block with intrathecal spinal morphine. Subjects were able to speak, read, and write Thai. We excluded mothers with medical complications (diabetes mellitus, severe hypertension), serious intraoperative and postpartum complications (early postpartum hemorrhage, pelvic organ injury), abnormal breasts and nipples, contraindications for breastfeeding (maternal Human Immunodeficiency Virus (HIV) infection), postpartum mother-infant separation, neonatal birth weight < 2,500 g, birth

asphyxia (Apgar score at 1 min ≤ 7), tongue-tied, cleft lip or cleft palate.

Women who planned to undergo cesarean delivery were informed about the study, and ten steps to successful breastfeeding in the labor room[16]. Written informed consent was obtained from each participant before enrollment. At 2 hours after the operation, post-cesarean women with infants who met the eligibility criteria were randomized into two groups: electric breast pump and conventional breastfeeding by using a computer-generated list and allocation concealment by sequentially opaque envelopes. Each group was assigned to a different postpartum ward to preclude cross-talk contamination.

The electric breast pump group received a double collection electric breast pump (Spectra®Dew 350, Uzinmedicare Co.) and were instructed in steps of its use by trained physicians and nurses who not involved in the study. The steps of operation were started by putting breast shields cover both breasts with the suction setting at 100 mmHg then gradually increasing as tolerated. The cycling rate was 48 cycles/min, duration 15 min, interval 3 hours after breastfeeding (8 times in 24 hours). The conventional breastfeeding group breastfed on demand at least 8 times in 24 hours. The electric breast pump group used the electric breast pump until the women had any signs and/or symptoms of OL. All participants were informed about the signs and symptoms of OL via maternal perceptions, including breast fullness, breast tingling, and milk leakage. A personal digital clock with a standard time setting was provided for recording the time to OL when the mother noticed any signs and/or symptoms of OL. Ward nurses reminded the mothers of the signs and symptoms of OL three times a day. Women who had delayed OL after discharge were followed-up via telephone so as to record time to OL. Maternal nipple pain was immediately evaluated by numerical pain score (0-10) after each pump in the electric breast pump group and after each breastfed in conventional breastfeeding group in the first 24 hours. Baseline characteristics of maternal outcomes and neonatal outcomes, time to initiate breastfeeding and length of hospital stay were recorded.

The sample size was calculated based on a pilot study with a power of 90% and a dropout rate of 10%. Thirty-four participants (17 in each group) were recruited. Data were analyzed by Stata version 13. The student t-test and Mann–Whitney U test were used to compare continuous variables depending on the normality of distribution between groups. The results were presented as means and standard deviations or medians and interquartile ranges. The Fisher's exact and chi-squared tests were used to compare categorical variables as appropriate, and the results were presented as numbers and percentages. The cumulative rate of time to OL by maternal perception was analyzed using a survival analysis. A p value < 0.05 was considered statistically significant.

Results

Between February 7 and March 27, 2020, 53 eligible post-cesarean women who had undergone spinal block with intrathecal spinal morphine were enrolled in the study. Of these, 19 women were excluded from the study: 3 because of serious medical conditions (uncontrolled diabetes mellitus, severe hypertension, and venous sinus thrombosis), 3 because of contraindications for breastfeeding (2 HIV infection and 1 maternal amphetamine use), 12 because of mother-infant separation (11 due to respiratory distress and 1 due to diaphragmatic hernia), and 1 cleft lip. Thus, a total of 34 eligible women were randomly assigned to the electric breast pump group and the conventional breastfeeding group: 17 for each group. There were no dropouts (Fig. 1). Baseline characteristics were similar between groups, including gestational age, body mass index (pre-pregnancy, pre-delivery), parity, indication for cesarean section, operative time, time to initiate breastfeeding, frequency of breastfeeding, frequency of breast pump until time to OL, and neonatal characteristics (Table 1).

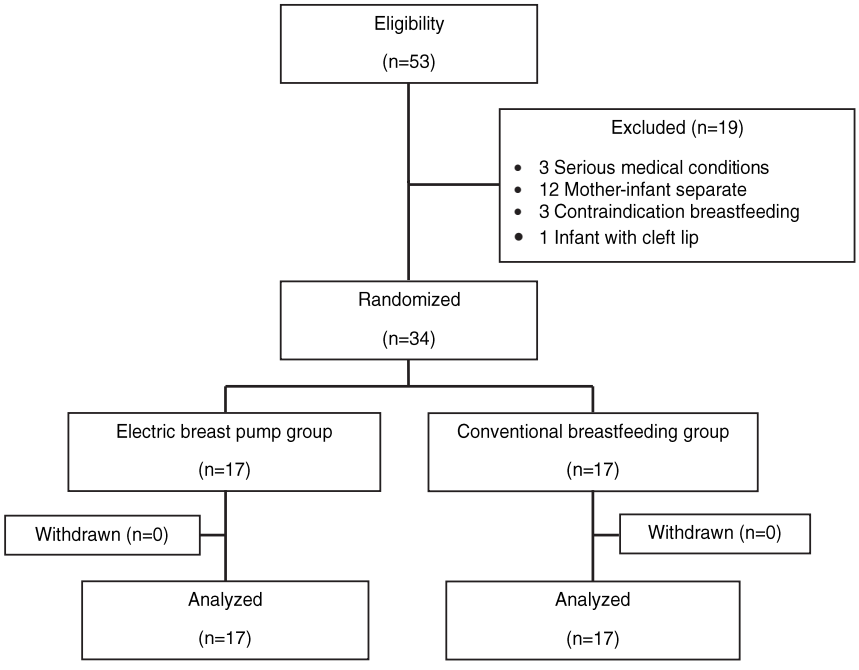


Fig. 1. Study flow.

Table 1. Baseline characteristics.

Demographic profile	Electric pump (n = 17)	Conventional (n = 17)	p value
Maternal characteristics			
GA (days), mean ± SD	273 ± 6.7	267 ± 5.3	0.13
BMI (kgs/m^2), mean ± SD			
Pre-pregnancy	25.6 ± 5.3	25.5 ± 7.9	0.97
Pre-delivery	31.5 ± 5.0	29.2 ± 5.5	0.20
Parity			0.15
Primipara, n (%)	8 (47.1)	4 (23.6)	
Multipara, n (%)	9 (52.9)	13 (76.4)	
Indication for cesarean section, n (%)			0.29
Cephalopelvic disproportion	8 (47.1)	3 (17.6)	
Previous cesarean section	7 (41.1)	12 (70.6)	
Abnormal presentation	1 (5.9)	1 (5.9)	
Other	1 (5.9)	1 (5.9)	
Operative time (min), mean ± SD	47.4 ± 13.4	46.8 ± 13.7	0.90
Time to initiate breastfeed (min), mean ± SD	156.3 ± 41.4	184.5 ± 96.3	0.27
Frequency of breastfeeding (times/day), mean ± SD	16.0 ± 2.7	15.5 ± 2.2	0.53
Frequency of breast pumps until time to OL (times), mean ± SD	13.8 ±3.2	N/A	
Neonatal characteristics			
Neonatal birth weight (g), mean ± SD	3337.1 ± 356.6	3197.6 ± 378.8	0.27
APGAR score at 1 min, mean ± SD	8.1 ± 0.4	8.3 ± 0.5	0.13

GA: gestational age, BMI: body mass index, SD: standard deviation, n: number of patients, OL: onset of lactation, N/A: non applicable

Time to OL by maternal perception was the primary outcome and was 43.8 ± 11.0 hours and 68.3 ± 19.9 hours in the electric breast pump group and conventional group, respectively. The mean difference was -24.5 (95% CI -35.7 to -13.8), p < 0.001. The time to OL in the electric breast pump group was mostly (70.6%) by day 2 while it was mostly (52.9%) by day 3 in the conventional breastfeeding group albeit 6 women (35.3%) had delayed OL (Table 2). The cumulative rate of time to OL between groups is shown in Fig. 2. The median time to OL in the electric breast pump group was 41 hours compared to 63 hours in the breastfeeding group.

Table 2. Time to OL.

Time to OL	Electric pump (n = 17)	Conventional (n = 17)	Mean difference	95%CI	p value
OL by mean ± SD, h	43.8 + 11.0	68.3 + 19.9	-24.5	-35.7, -13.8	< 0.001
OL by day of postpartum, h					
Day 1, n (%)	0	0			
Day 2, n (%)	12 (70.6)	2 (11.8)			
Day 3, n (%)	5 (29.4)	9 (52.9)			
> Day 3, n (%)	0	6 (35.3)			

OL: onset of lactation, CI: confidence interval, SD: standard deviation, n: number of patients

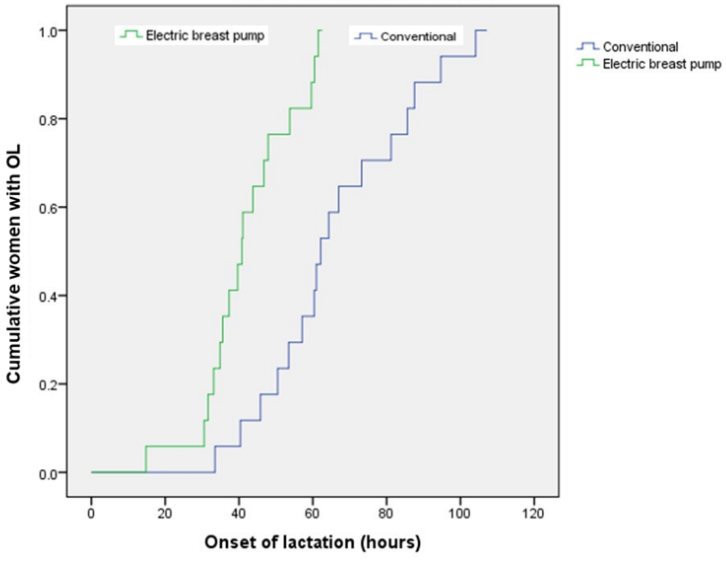


Fig. 2. Cumulative rate of time to onset of lactation.

Maternal and neonatal outcomes are presented in Table 3. Maternal nipple pain was 3.0 (0, 6) and 3.0 (0, 7) in the electric breast pump group and the conventional breastfeeding group, respectively (p = 0.74). There was no significant difference in maternal nipple abrasion between groups. There was no neonatal excessive weight loss (> 10% of birth weight) in either group. Two neonates in the conventional breastfeeding group had early jaundice due to glucose-6-phosphate Dehydrogenase deficiency and ABO incompatibility. The length of hospital stay was similar between groups.

Table 3. Secondary outcomes.

Outcomes	Electric pump (n = 17)	Conventional (n = 17)	p value
Nipple pain score, median (IQR)	3 (0, 6)	3 (0, 7)	0.74
Nipple abrasion, n (%)	4 (23.5)	3 (17.6)	0.67
Length of stay (days), mean ± SD	2.8 ± 0.1	2.9 ± 0.2	0.88
Neonatal jaundice, n (%)	0	2 (11.8)	0.48

IQR: interquartile range, SD: standard deviation, n: number of patients

Discussion

The present study aimed to evaluate the efficacy of an electric breast pump compared with conventional breastfeeding in promoting time to OL in post-cesarean women who had undergone spinal block. The electric breast pump group had 24.5 hours faster OL by maternal perception over against the conventional breastfeeding group (43.8 hours versus 68.3 hours, respectively). This result was similar to Zhang et al who reported that the electric breast pump group in post-cesarean women had a 17-hour faster OL according to test weighing (52.2 hours versus 70.6 hours, respectively)[14]. More than two-third of post-cesarean women in the electric breast pump group had OL by the second postpartum day, and the remainder had OL by the third postpartum day. By comparison, half of the conventional breastfeeding group had OL by the third postpartum day, and one-third of them had delayed OL. The results of the current study support the hypothesis that the electric breast pump stimulates breast milk production and shortens the time to OL in women who undergo a cesarean section. To contrast, Chapman et al indicated that the electric breast pump had no beneficial effect on OL as measured by infant weight before and after breastfeeding in post-cesarean women. Chapman, et al, however, used the electric breast pump only 3 times a day (maximum 45 min/day)[7]. Slusher et al suggested that mothers who used an electric breast pump fewer than four times daily with a total time less than 70 min per day had no increased in milk volume[12]. This might be explained by the efficacy of the electric breast pump used for 15 min every 3 hours or 8 times a day in the current study (120 min), which had a positive effect on faster OL. Thus, the frequency and duration of electric breast pump affected time to OL.

Test weighing the infant is the gold standard for evaluating OL; however, this method is not practicable for general use. This conclusion is supported by a study by Zhang et al in which evaluated time to OL by testing weighing only during the day time but such an approach may have affected the accuracy of time to OL[14]. In addition, this method depends on breastfeeding episodes and need slightly sensitive scale equipment that may not be available in low resource settings. Maternal perception of OL is practicable and could be used instead of test weighing because mothers can and do notice their lactation, all day and night. Notably, the technique is low-cost and could be used to evaluate time to OL after discharge. Chapman et al likewise studied the validity of time to OL to indicate lactogenesis II comparing between test weighing and maternal perception in post-cesarean women and concluded that maternal perception of the OL was a valid public health indicator of lactogenesis stage II[7].

Secondary outcomes indicated mild nipple pain in both groups without serious events related to the electrical breast pump. The current study reported that nipple abrasion mostly occurred within 24 hours postpartum at the tip of nipple as a result of improper latch-on[17]. An electric breast pump can cause nipple abrasion but is commonly located at the side of the nipple due to rubbing against the breast shield tunnel during breast pump[18]. The current study showed that the electric breast pump did not increase nipple pain and did not cause nipples trauma. There were no maternal complications in either group, and length of hospital stay was not significantly different between

groups. Excessive weight loss (> 10 %) was not found in our study because the infant formula was given to babies whose weight loss was 8% or more so as to prevent neonatal detrimental events (1 in the electric breast pump group and 3 in the conventional breastfeeding group).

The electric breast pump benefitted post-cesarean women at risk of delayed OL because of postoperative pain and fatigue by shortening the time to OL. The electric breast pump can also be used to stimulate breast milk production in mothers facing health issues or mother-infant separation, and/or improper latch-on or suckling problems. OL is the first time that mothers have confidence that they have enough breast milk to nurse their babies. Women with delayed OL have an increased risk of milk insufficiency and early infant formula supplementation, increasing the risk of cow milk protein allergy[19]. Women with early OL have, moreover, a longer exclusive breastfeeding duration compared with women with delayed OL[20].

The strength of the current study was that it was a randomized controlled trial. We minimized possible potential confounders by separating each group into different wards to prevent cross-talk contamination. We standardized the electric breast pump use by providing training by staff who not involved in the study. We also regularly reminded mothers about the signs and/or symptoms regarding time to OL. For further research, the study in mother-infant separation should be considered in terms of the role of the electric breast pump to promote breastfeeding in this group.

Conclusion

Post-cesarean women in the electric breast pump group had significance earlier time to OL when compared with conventional breastfeeding group.

Acknowledgements

The authors would like to thank (a) the participating mothers, (b) the nursing staff and physicians for their service, and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Gartner LM, Morton J, Lawrence RA. Breastfeeding and the use of human milk. Pediatrics 2005;115:496-506.
2. Victora CG, Horta BL, Barros FC. Association between breastfeeding and intelligence, educational attainment, and income at 30 years of age: a prospective birth cohort study from brazil. Lancet Glob Health 2015;3:e199-e205.
3. World Health Organization. Exclusive breastfeeding for six months best for babies everywhere [internet]. 2011 [cite 2019 May 5]. Available from: http://www.who.int/mediacentre/news/statements/2011/breastfeeding_20110115/en/
4. United Nations Children's Fund. Breastfeeding a mother's gift for every child. UNICEF [internet]. 2018 [cite 2019 May 5]:1-5. Available from: https://www.unicef.org/publications/files/UNICEF_Breastfeeding_A_Mothers_Gift_for_Every_Child.pdf
5. Chapman DJ, Pérez ER. Identification of risk factors for delayed onset of lactation. J Am Diet Assoc1999;99:450-4.
6. Pillay J, Davis TJ. Physiology Lactation [internet]. Stat Pearls Publishing; 2019 [cite 2019 May 15]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK499981/
7. Chapman DJ, Pérez ER. Maternal perception of the onset of lactation is a valid, public health indicator of lactogenesis stage II. J Nutr 2000;130:2972–80.
8. Intarasukum P. Onset of lactation after an uncomplicated cesarean delivery: a study between emergency cesarean delivery and elective cesarean delivery. J Health Sci 2014;23:1058-66.
9. Jeerasap R, Phaiboonbunpot N, Panikom S. Routes of delivery and onset of lactation. J Health Sci 2010;19:270-8.
10. Prior E, Santhakumaran S, Gale C, Philipps LH, Modi N, Hyde MJ. Breastfeeding after cesarean delivery: a systemic review and meta-analysis of world literature. Am J Clin Nutr 2012;95:1113-35.
11. Albokhary AA, James JP. Does cesarean section have an impact on the successful initiation of breastfeeding in Saudi Arabia. Saudi Med J 2014;35:1400-3.
12. Slusher T, Slusher IL, Biomdo M, Thomas FB, Curtis BA, Meier P. Electric breast pump use increases maternal milk volume in African nurseries. J Trop Pediatr 2007;53:125-30.
13. Fewtrell MS, Kennedy K, Ahluwalia JS, Nicholl R, Lucas A, Burton P. Predictors of expressed breast milk volume in mothers expressing milk for their preterm infant. Arch Dis Child Fetal Neonatal Ed 2016;101:F502-6.

14. Zhang F, Yang Y, Bai T, Sun L, Sun M, Shi X, et al. Effect of pumping pressure on onset of lactation after cesarean section: A randomized controlled study. Matern Child Nutr 2018;14:e12486.
15. World Health Organization. WHO statement on cesarean section rates [internet]. 2015 [cite 2019 May 5]:1-8. Available from: https://apps.who.int/iris/bitstream/handle/10665/161442/WHO_RHR_15.02_eng.pdf?sequence=1
16. World Health Organization. Ten steps to successful breastfeeding [internet]. 2016 [cite 2019 May 5]. Available from: http://www.who.int/activities/promoting-baby-friendly-hospitals/ten-steps-to-sucessful-breastfeeding.
17. Branger B. Description of 101 cases of nipple cracks and risk factors via case-control study in eight units of a perinatal network. Arch Pediatr 2020;27:45-50.
18. Bonyata K. Healing tips for nipple cracks or abrasion [internet]. Michigan; 2018 [cited 2020 Jun 10]. Available from: https://kellymom.com/bf/concerns/mother/nipplehealing/
19. Kelly E, DunnGalvin G, Murphy BP, Hourihane JB. Formula supplementation remains a risk for cow's milk allergy in breast-fed infants. Pediatr Allergy Immunol 2019;30:810-6.
20. Hruschka DJ, Sellen DW, Stein AD, Martorell R. Delayed onset of lactation and risk of ending full breast-feeding early in rural Guatemala. J Nutr 2003;133:2592-9.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 109-119

OBSTETRICS

Hot Patch Applied to the Lower Back for Pain Relief during the Active Phase of the First-stage Labor: A randomized controlled trial

Chanakarn Suthisuntornwong, M.D.*,
Thumwadee Tangsiriwatthana, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To determine the efficacy of hot patch for pain relief during the active phase of the first stage labor.

Materials and Methods: Fifty-eight singleton pregnant women undergoing normal delivery at Khon Kaen Hospital between February 5 and May 30, 2020, were randomly assigned into two groups: hot patch and standard care. The hot patch was applied to the lower back (dermatome T10 to L1) when cervix dilatation reached 4-6 cm until fully dilated. Pain scores were recorded before hot patch application and every hour until the end of the first stage labor.

Results: Baseline characteristics were not significantly different between groups ($p > 0.2$). The mean pain score of the hot patch group was significantly less than the control group at 1, 2, 3, 4, and 5 hours after intervention (4.4 ± 1.9 vs. 6.4 ± 1.8, 5.6 ± 2.2 vs. 7.4 ± 1.3, 5.4 ± 1.8 vs. 8.1 ± 0.8, 5.7 ± 2.2 vs. 8.4 ± 0.7, 8.0 ± 0.0 vs. 8.7 ± 0.5, $p < 0.001$, respectively). The mean duration of the active phase of the first stage labor in the hot patch group was significantly < 0.001). There was no adverse event found.

Conclusion: A hot patch applied to the lower back significantly reduced labor pain during the first stage labor.

Keywords: hot patch, non-pharmacologic, labor pain.

Correspondence to: *Chanakarn Suthisuntornwong, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. E-mail: pre.cnk@gmail.com*

Received: 30 September 2020, **Revised:** 20 November 2020, **Accepted:** 28 December 2020

การใช้แผ่นแปะร้อนบริเวณหลังส่วนล่างเพื่อบรรเทาอาการปวดในช่วงระยะแรกของการเจ็บครรภ์คลอดจริง: การทดลองแบบสุ่ม

ชนากานต์ สุทธิสุนทรวงศ์, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลของการใช้แผ่นแปะร้อนเพื่อลดอาการปวดในช่วงเวลาปากมดลูกเปิดเร็วของการคลอดระยะที่หนึ่ง*

วัสดุและวิธีการ: *หญิงตั้งครรภ์เดี่ยวจำนวนห้าสิบแปดคน ที่จะคลอดบุตรโดยวิธีธรรมชาติในโรงพยาบาลขอนแก่นระหว่างวันที่ 5 กุมภาพันธ์ ถึง 30 พฤษภาคม 2563 ได้รับการสุ่มออกเป็นสองกลุ่ม: กลุ่มแปะแผ่นร้อน และกลุ่มดูแลตามมาตรฐาน แผ่นแปะร้อนใช้บริเวณหลังส่วนล่าง (เดอร์มาโทม T10 ถึง L1) เริ่มที่ปากมดลูก 4-6 เซนติเมตร จนปากมดลูกเปิดขยายหมด คะแนนความเจ็บปวดถูกบันทึกก่อนการใช้แผ่นแปะร้อน และทุกๆ ชั่วโมง จนสิ้นสุดระยะแรกของการเจ็บครรภ์คลอด*

ผลการศึกษา: *ลักษณะพื้นฐานประชากรไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างสองกลุ่ม ($p > 0.2$) คะแนนความเจ็บปวดเฉลี่ยของกลุ่มแผ่นแปะร้อนน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญที่ 1, 2, 3, 4 และ 5 ชั่วโมง ตามลำดับ (4.4 ± 1.9 และ 6.4 ± 1.8, 5.6 ± 2.2 และ 7.4 ± 1.3, 5.4 ± 1.8 และ 8.1 ± 0.8, 5.7 ± 2.2 และ 8.4 ± 0.7, 8.0 ± 0.0 และ 8.7 ± 0.5, $p < 0.001$ ตามลำดับ) ระยะเวลาเฉลี่ยของช่วงปากมดลูกเปิดเร็วของการคลอดระยะที่หนึ่งในกลุ่มแปะแผ่นร้อนน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (138.5 ± 63.1 และ 222.7 ± 82.3, $p < 0.001$) และไม่พบเหตุการณ์ไม่พึงประสงค์*

สรุป: *การใช้แผ่นแปะร้อนบริเวณหลังส่วนล่างช่วยบรรเทาอาการปวดในช่วงระยะแรกของการเจ็บครรภ์คลอดได้อย่างมีนัยสำคัญ*

คำสำคัญ: *แผ่นแปะร้อน, การบรรเทาอาการปวดที่ไม่ใช้ยา, ภาวะเจ็บครรภ์คลอด*

Introduction

Labor is unpredictable and is one of the most painful experiences for women. Approximately forty percent of women identify labor pain as the worst part of childbirth[1]. The longer the interval of uterine contractions, the deeper and more emotional stress experienced. Eighty-three percent of pregnant women used one or more pain medications during birthing whereas 17% do not require any[1].

There are two kinds of pain during labor, visceral and somatic. Visceral pain occurs during the early first stage and the second stage labor, while somatic pain occurs during the late first stage and second stage[2].

Pain from uterine contractions is referred to the dermatomes which are supplied by T10, T11, T12, and L1. As labor progresses, the pain becomes more severe and is referred to the abdomen, lower lumbar, and upper sacrum, areas supplied by T10 and L1[2]. A release of stress hormones such as cortisol and beta-endorphin can trigger pain, stress, and anxiety, which can adversely affect uterine activity and uteroplacental blood flow. Effective analgesia attenuates or eliminates these responses[3]. Several pain control methods have been studied and some of them have been used for decades, including pharmacological and non-pharmacological (e.g., opioids administration, epidural analgesia, nitrous oxide inhalation, massage, heat or cold therapy, transcutaneous electrical nerve stimulation (TENS), yoga, breathing exercise, reflexology, and music therapy).

According to a Cochrane review of pharmacological methods, epidural analgesia is an effective way of providing pain relief. The negative effects of epidural analgesia have, however, been reported, including a prolonged first and second stage of labor and increased oxygen use, malrotation, instrumental delivery, and cesarean section especially for dystocia[4]. As for non-pharmacological methods, massage, warm pack, and thermal manual methods were found to play a role in pain relief, reducing duration of labor and emotional experience improved with safety. Further high quality research is needed to address these outcomes and to determine the effectiveness of these methods for pain control[5].

One of the non-pharmacologic methods for labor pain reduction is heat therapy; it is simple, inexpensive, and readily available with few side effects[6]. The terminals of small A delta and C afferent nerve fibers act as receptors for nociception from superficial structures (skin and subcutaneous tissue), deep structures (muscle, fascia), and viscera[2]. When tissue injury occurs, a large amount of various chemical mediators are liberated. These include hydrogen ions, noradrenaline, bradykinine, histamine, and potassium ions[7]. Heat may stimulate heat receptors in dermal and deeper tissues. Based on the gate control theory[8], different impulses neutralize themselves at the level of spinal cord by leading to a closure of the gate and subsequently impeding neural impulses from reaching the brain. The other effect of heat therapy possibly shortens the duration of labor[9]. Khamis et al showed that heat induces a significant increase in uterine activity without causing any abnormal fetal heart change[10] and releases endorphins[11]. In addition, heat can stimulate touch and temperature receptors which promote a pleasure feeling and decrease the level of pain[12]. The optimum temperature range for superficial heat therapy is between 40 and 45°C[13].

To our knowledge, the intensity of labor pain increases when cervical progression especially when in active phase. Therefore, we started the intervention at 4-6 cm which is in the phase of maximum slope according to Friedman's curve which cervix is rapidly progress and cause severe labor pain. In the current study, we used a Japanese iron-filled hot patch. When exposed to the air, the iron oxidizes and heats up in about 10 min, and stays warm for about 10 hours. Air-activated hot patches generate heat up to 50°C. The natural therapeutic heat will last for 10 hours. Blood flow is increased by warming the affected area and inducing

vasodilatation which increases the supply of oxygen and removal of metabolic waste, leading to better healing and reduced pain[14].

According to a Cochrane review, evidence regarding the efficacy of heat therapy for pain relief with a warm pack and a warm towel in the first stage labor remains insufficient[5]. We thus planned to study the efficacy of the Japanese iron-filled hot patch given its simplicity, affordability, and availability in drug and/or convenience stores.

Materials and Methods

We recruited pregnant women 18 or older who had their labor at Khon Kaen Hospital between February 5 and May 30, 2020. All eligible pregnant women gave informed consent before enrolling in the study. Inclusion criteria were: age 18 or older, being at the beginning of the active phase of labor (cervical dilation between 4 and 6 cm), gestational age between 37 and 41 weeks, singleton, low-risk pregnancy, and cephalic presentation. The exclusion criteria were: any abnormal patterns of external fetal heart rate monitoring, history of chronic pelvic pain, and/or cutaneous lesion(s) involving the lower back.

The study was reviewed and approved by the Khon Kaen Hospital Institute Review Board in Human Research. The randomization list was kept in a sealed opaque envelope. The sealed opaque envelopes were opened by residents or nurses at the labor room after the participants were enrolled in the study. The participants were randomly allocated into two groups by computer-generated randomization using block of four. Group 1: Japanese iron-filled hot patch was applied to the lower back; Group 2: no Japanese iron-filled hot patch. Both groups received the same intrapartum standard care. The intervention started from the beginning of the active phase (cervical dilatation 4-6 cm). For the Japanese iron-filled hot patch, a 9x12 cm, 40-45 °C Japanese iron-filled hot patch was placed on the patient's clothing over the lower back (dermatome T10 to L1). Skin temperature and appearance at hot patch placement was monitored every 1 hour by thermoscan (Xiaomi mijia iHealth thermometer, China). The Japanese iron-filled hot patch will be immediately removed if there is any abnormal skin reaction (clear water blisters, redness, or loss of sensation). In the control group, standard care with no Japanese iron-filled hot patch was provided. Pain scores were recorded by residents on service at the labor room, using a visual analogue scale (VAS). A horizontal line, 10-cm in length, with the descriptive words "no pain" and "worst pain" at each end. Participants were asked to put a mark on the line at the point that represented the most severe pain that they experienced before the intervention (cervix dilated 4-6 cm), and every 1 hour until full cervical dilatation. The two groups received routine nursing care including vital signs were recorded every 4 hours, uterine contractions and fetal heart were recored every 30 minutes. Vaginal examinations were performed every 2 hours by residents. Additional pain control with pethidine 50 mg intramuscularly injection every 4 hours was provided for all participants when needed. At the end of delivery, participants' satisfaction of the hot patch application was recorded by using the questionnaire.

The primary outcome was pain scores during the active phase of labor comparing between the Japanese iron-filled hot patch and no Japanese iron-filled hot patch. The secondary outcomes were (a) the duration of the active phase of the first-stage labor, (b) route of delivery, (c) adverse events, (d) participant satisfaction, and (e) skin temperature.

The sample size was based on the data from a pilot study with 90% power and a 5% dropout rate. The appropriate sample size was thus 58 participants 29 in each group. Data were analyzed using repeated measures by the generalized estimating equation (GEE). Continuous variables were analyzed using the student t-test and presented as means and standard deviation (SD). Categorical variables were analyzed using the chi-square and Fisher's exact test and presented as percentages. The mean difference of the pain score between groups was analyzed and presented with 95% confidence intervals. A p value < 0.05 was considered statistically

significant.

Results

Sixty eligible pregnant women were enrolled, two were excluded due to abnormal fetal heart rate and pregnancy-induced hypertension. The 58 participants were randomized into 29 cases per group (Fig. 1). Three from each group withdrew from the study before recording the pain data because they were diagnosed as having cephalopelvic disproportion and fetal distress so a cesarean section was performed. Ultimately, 26 subjects in each group were included for analysis.

The demographic and obstetric variables (mean age, gestational age, body mass index (BMI), parity, pain score (VAS) before intervention) were similar between groups (Table 1).

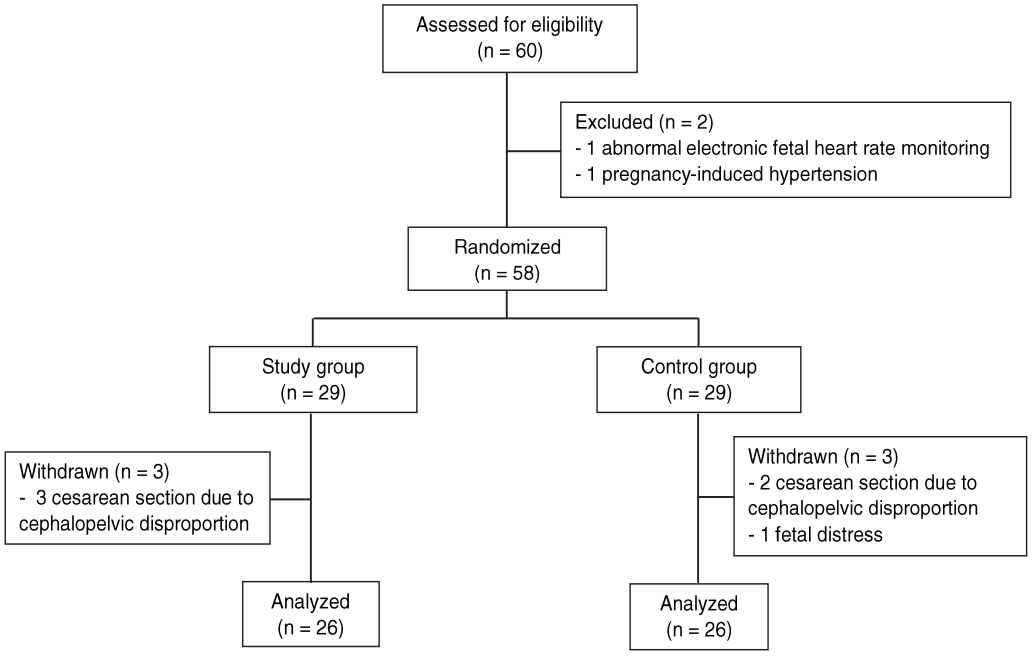


Fig. 1. Study flow diagram.

Table 1. Demographics and characteristics of the cases.

Characteristic	Hot patch group (n = 26) mean ± SD	Standard care group (n = 26) mean ± SD	p value
Age (years)	26.7 ± 4.9	25.1 ± 5.4	0.28[b]
Gestational age (weeks)	39^{+1} ± 0.9	39^{+2} ± 1.0	0.66[b]
Parity, n (%)			
- Nulliparous	12 (46.2)	12 (46.2)	1.00[a]
- Multiparous	14 (53.8)	14 (53.8)	
Maternal BMI (kg/m^2)	28.1 ± 3.3	26.9 ± 3.7	0.23[b]
Pain score (VAS) before intervention	4.7 ± 0.9	5.2 ± 2.3	0.26[b]

[a] chi-square test, [b] student t-test

BMI: body mass index, SD: standard deviation, VAS: visual analogue scale

The respective mean pain score in the control and Japanese iron-filled hot patch group are shown in Table 2. The primary outcome was pain scores during the active phase of the first stage labor, which was recorded every hour after intervention. There was a significant difference in labor pain reduction between the Japanese iron-filled hot patch group and the control group ($p < 0.001$) (Table 2, Fig. 2). Pain perception among the nulliparous women in the Japanese iron-filled hot patch group was lower than in the control group at 1, 2, 3, 4, and 5 hours after intervention ($p < 0.001$) (Table 3, Fig. 3). The multiparous pain score was lower in the Japanese iron-filled hot patch at 1, 2, 3, and 4 hours ($p < 0.001$) (Table 4, Fig. 4). Regularly uterine contractions before and during the intervention were observed in both groups. None of the participant requested for additional pain control.

Table 2. Pain score (VAS) in the active phase of the first stage labor.

	Hot patch group (n = 26) mean ± SD	**Standard care group (n = 26) mean ± SD**	**mean difference**	**95%CI**	**p value**
1 hour	4.4 ± 1.9 (n = 26)	6.4 ± 1.8 (n = 26)	- 1.32	- 2.11 to - 0.52	0.001[c]
2 hours	5.6 ± 2.2 (n = 20)	7.4 ± 1.3 (n = 26)			
3 hours	5.4 ± 1.8 (n =12)	8.1 ± 0.8 (n = 21)			
4 hours	5.7 ± 2.2 (n = 5)	8.4 ± 0.7 (n = 16)			
5 hours	8.0 ± 0.0 (n = 1)	8.7 ± 0.5 (n = 3)			

[c] Generalized estimation equation (GEE), VAS: visual analogue scale, SD: standard deviation, CI: confidence interval

Table 3. Nulliparous pain score (VAS).

	Hot patch group (n = 12) mean ± SD	**Standard care group (n = 12) mean ± SD**	**mean difference**	**95%CI**	**p value**
1 hour	3.9 ± 1.0 (n = 12)	6.8 ± 1.9 (n = 12)	- 1.41	- 1.99 to - 0.84	< 0.001[c]
2 hours	5.6 ± 2.2 (n = 12)	7.7 ± 1.4 (n = 12)			
3 hours	5.8 ± 1.5 (n = 7)	8.0 ± 0.8 (n = 11)			
4 hours	7.1 ± 0.8 (n = 2)	8.3 ± 0.6 (n = 9)			
5 hours	8.0 ± 0.0 (n = 1)	8.7 ± 0.6 (n = 3)			

[c] Generalized estimation equation (GEE), VAS: visual analogue scale, SD: standard deviation, CI: confidence interval

Table 4. Multiparous pain score (VAS).

	Hot patch group (n = 14) mean ± SD	**Standard care group (n = 14) mean ± SD**	**mean difference**	**95%CI**	**p value**
1 hour	4.8 ± 2.3 (n = 14)	6.1 ± 1.7 (n = 14)	- 1.31	- 2.1 to - 0.51	0.001[c]
2 hours	5.7 ± 2.9 (n = 8)	7.3 ± 1.2 (n = 14)			
3 hours	5.0 ± 2.4 (n=5)	8.2 ± 0.9 (n = 10)			
4 hours	4.3 ± 2.5 (n=3)	8.5 ± 0.9 (n = 7)			

[c] Generalized estimation equation (GEE), VAS: visual analogue scale, SD: standard deviation, CI: confidence interval

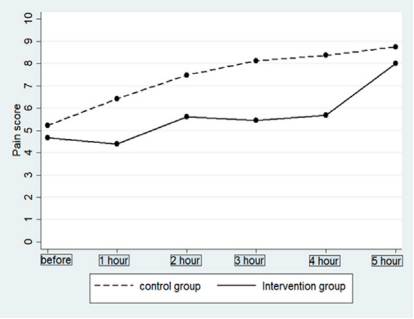


Fig. 2. Pain score visual analogue scale in the active phase of the first stage labor.

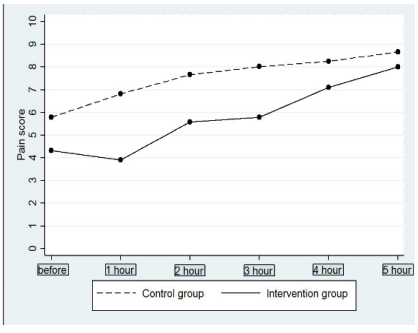


Fig. 3. Nulliparous pain score visual analogue scale in the active phase of the first stage labor.

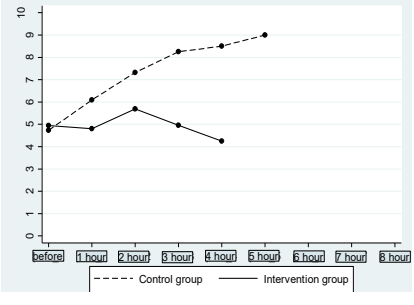


Fig. 4. Multiparous pain score visual analogue scale in the active phase of the first stage of labor.

Secondary outcomes showed that the mean duration of the active phase of the first stage labor in the Japanese iron-filled hot patch group was 138.5 ± 63.1 vs. 222.7 ± 82.3 min in the control group, with a mean difference of 84.3 min shorter in the Japanese iron-filled hot patch group. There was one woman in the control group who had arrest of descent after full cervical dilatation so a cesarean section was performed. In the Japanese iron-filled hot patch group, skin temperature was maintained at between 41 and 43°C during the intervention without any adverse event. All of the participants in the Japanese iron-filled hot patch group were satisfied with the intervention (Table 5). The duration of the first stage labor in the Japanese iron-filled hot patch was significantly reduced in both nulliparous and multiparous women ($p = 0.004$, $p = 0.006$) (Table 6).

Table 5. Secondary outcomes.

	Hot patch group (n = 26) mean ± SD	Standard care group (n = 26) mean ± SD	mean difference (95%CI)	p value
Duration of the active phase of the first-stage labor (minutes)	138.5 ± 63.1	222.7 ± 82.3	- 84.3 (- 125.1 to - 43.4)	< 0.001[b]
Adverse events, n (%)				
- Skin burn	0 (0.0)			
- Skin allergy	0 (0.0)			
Route of delivery, n (%)				0.32[d]
- Vagina	26 (100)	25 (96.2)		
- Cesarean section	0 (0)	1 (3.8)		
Skin temperature (°C)				
At 0 hour	41.6 ± 0.6			
At 1 hour	42.2 ± 0.6			
At 2 hours	42.6 ± 0.9			
At 3 hours	42.8 ± 0.7			
At 4 hours	43.1 ± 0.5			
Maternal satisfaction	100%			

[b] student t-test, [d] Fisher's exact test, SD: standard deviation, CI: confidence interval.

Table 6. Duration of the active phase of the first stage labor.

	Hot patch group (n = 26) mean ± SD	Standard care group (n = 26) mean ± SD	mean difference	95%CI	p value
Nulliparous	**(n = 12)**	**(n = 12)**			
	160.4 ± 51.3	255.4 ± 90.5	- 95.0	- 157.3 to - 32.7	0.004[b]
Multiparous	**(n = 14)**	**(n = 14)**			
	119.6 ± 67.9	194.6 ± 65.3	- 75.0	- 126.7 to - 23.3	0.006[b]

[b] student t-test, SD: standard deviation, CI: confidence interval.

Discussion

The present study showed that the Japanese iron-filled hot patch group had a lower labor pain score than the control group. The finding was consistent with those of Behmanesh et al who reported a significant difference in labor pain between the heat and control groups in the first and second stage[9]. Many studies have shown that various forms of heat therapy (warm bag, warm water, and immersion) significantly reduced labor pain in the first stage labor[9, 15-16]. Lenstrup et al, studied the effects of warm tub bathing during labor and found that pain relief and cervical dilatation trended greater with a warm bath albeit there was no statistically significant difference[17]. Recent studies have shown that the effect of heat in various forms in reducing labor pain and raising mother satisfaction[9, 18-19].

According to the previous studies of non-pharmacologic methods, the aim of the studies was to avoid invasive pharmacological methods of pain management in labor. They did not provide any additional pain killer in both groups. Taavoni et al, revealed that warm packs to the sacrum and perineum

during active phase of the first stage labor reduced pain and improved maternal satisfaction and they performed only reclining position without ambulation and any other intervention in control group[19]. Lee et al, studied in warm showers reported significantly lower VAS scores at 4-cm and 7-cm cervical dilations than the control group ($p < 0.01$) and no other pharmacologic drug added, except those for induction of labor[18]. Shirvani et al revealed that the degree of pain during acceleration phase was significantly lower in cold therapy group than in control group ($p < 0.02$) as well as during the maximum of slope, deceleration phase and the second stage of labor with $p = 0.0001$, no other pain-relieving method was applied in control group in order to eliminate the effect of supporter factor[20]. Ganji et al studied local warming with intermittent cold pack versus routine care on labor pain and founded that the difference in pain severity at the end of the acceleration phase was statistically significant lower in the intervention group ($p = 0.002$) and during the maximum of slope, the deceleration phase and the second stage with $p = 0.0001$[21]. This non-invasive, non-pharmacological modality provides a safe alternative for mother and fetus and also provides mothers with a choice if they would prefer to avoid invasive pharmacological methods of pain management in labor. This method may be particularly attractive to mothers who want to be more involved and in control of their own care. However, the current study provided additional pain control for the participants in both groups but none of them needed. In our institute, we give analgesic drug as needed, but most of them can tolerate labor pain and did not request for analgesia.

From these results, it seems that the form of heat can influence outcomes. Pain reduction might be related to heat mechanisms that cause endorphin hormone release as well as stimulating touch and temperature receptors which result in a feeling of pleasure and in pain relief. Some mechanisms include providing stimuli from peripheral sensory receptors to inhibit pain awareness, anti-nociceptive effects on the gate control system, decreasing muscle tension and distraction of attention from pain[22-24]. Heat therapy possibly increases the internal oxytocin, causing uterine contraction and decreased bleeding after delivery[9, 21]. In the current study average skin temperature was 41 to 43°C, which is within the optimum therapeutic range for heat treatment. Superficial heat, 1 cm from skin (i.e, 40 - 45°C) could relief pain by stimulate peripheral nerve and induce muscle relaxation without adverse effect to the fetus[13] (Fig. 5).

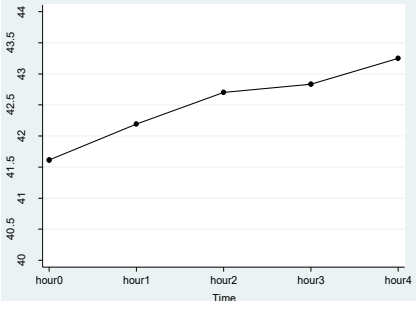


Fig. 5. Skin temperature (°C).

The present study included both nulliparous and multiparous while previous studies recruited only nulliparous[9, 19, 21]. The current study showed that both nulliparous and multiparous women who received the Japanese iron-filled hot patch had significantly lower labor pain than those who received standard care (Fig. 3, 4). Only moderate pain perception (pain score 4-6) was reported in either nulliparous or multiparous women

in the Japanese iron-filled hot patch group whereas the control group experienced severe pain (Fig. 2). Pain scores in the multiparous women in the hot patch group at 4 hours after intervention was lower than in the nulliparous ones. This might be from multiparous women had labor pain experience which cause different pain perception from nulliparous women who had not. In addition, when they received non-pharmacologic support such as hot patch, it could make they feel more comfortable from its effect of pain reduction and muscle relaxation. However, small sample size might cause bias these results.

The present study found that duration of the active phase of the first stage labor in the Japanese iron-filled hot patch group was significantly shorter than in the control group. This finding was comparable with a study by Khamis et al, who reported that heat increased uterine activity and so decreased the duration of labor without abnormal changes in the fetal heart rate[10]. Others studies have shown that warm water immersion decreased the duration of labor phases[25-26]. One study revealed that the duration of the first and third stages labor decreased significantly in the heat group compared to the control group[9].

Application of superficial heat therapy to manage labor pain is a convenient, effective and inexpensive method with few side effects. The method does not require high skill, provides relief and comfort, provides active participation of women in the birthing process, and promotes a more positive birth experience. Heat therapy should be used if desired[21]. All of the participants in the current study were satisfied with the hot patch and no serious adverse event were found.

The strengths of our study which make our results different from those of the previous studies were firstly, we monitored skin temperature to ensure that the temperature remained in the therapeutic range during intervention which plays an important role in regulating pain control. Secondly, we used repeated measure GEE to analyze pain score in the different time. Thirdly, both nulliparous and multiparous women were included into the study while the previous studies enrolled only the nulliparous ones. Lastly, we used hot patch which is the simply intervention with long duration that could maintain the longer heat effect than other forms of heat therapy. The limitation of present study was that we did not blind the intervention because the participants were in the same labor room.

Conclusion

A Japanese iron-filled hot patch applied to the lower back could significantly reduce labor pain in the active phase of the first stage labor.

Acknowledgements

The authors would like to thank (a) the participants for their co-operation, (b) staff, residents and nurses at the Labor Room, Khon Kaen Hospital for their kind help and support, and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Declercq ER, Sakala C, Corry MP, Applebaum S, Herrlich A. Major survey findings of listening to mothers SM III: pregnancy and birth. J Perinat Educ 2014;23:9-16.
2. Labor S, Maguire S. The pain of labour. Rev Pain 2008;2:15-9.
3. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al, editors. Williams obstetrics. 25th ed. New York: McGraw-Hill 2018:487.
4. Anim-Somuah M, Smyth R, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Syst Rev 2018;5:CD000331.
5. Smith CA, Levett KM, Collins CT, Dahlen HG, Ee CC, Suganuma M. Massage, reflexology and other manual methods for pain management in labour. Cochrane Database Syst Rev 2018;3:CD009290.
6. Simkin P, Bolding A. Update on nonpharmacologic approaches to relieve labor pain and prevent suffering. J Midwifery Women Health 2004;49:489-504.
7. Rowlands S, Permezel M. Physiology of pain in labour. Baillieres Clin Obstet Gynaecol 1998;12:347-62.
8. Habanananda T. Non-pharmacological pain relief in labour. J Med Assoc Thai 2004;87:S194-202.
9. Behmanesh F, Pasha H, Zeinalzadeh M. The effect of

heat therapy on labor pain severity and delivery outcome in parturient women. Iran Red Crescent Med J 2009;11:188-92.
10. Khamis Y, Shaala S, Damarawy H, Romia A, Toppozada M. Effect of heat on uterine contractions during normal labor. Int J Gynaecol Obstet 1983;21:491-3.
11. Bender T, Nagy G, Barna I, Tefner I, Kadas E, Geher P. The effect of physical therapy on beta-endorphin levels. Eur J Appl Physiol 2007;100:371-82.
12. Kuhtz-Buschbeck JP, Andresen W, Gobel S, Gilster R, Stick C. Thermoreception and nociception of the skin: a classic paper of Bessou and Perl and analyses of thermal sensitivity during a student laboratory exercise. Adv Physiol Educ 2010;34:25-34.
13. Poonperm R. Warm compression for pain relief during first stage of labor. J Royal Thai Army Nurses 2014;15: 23-7.
14. Jessying.com. review & give away : AMMELTZ YOKO YOKO heat patch for menstrual pain a non-medicated solution to period pain[Internet].2015. [cited 2019 Oct 20]. Available from:http://www.jessying.com/2015/03/review-giveaway-ammeltz-yoko-yoko-heat.html
15. Geissbuehler V, Stein S, EberhardJ. Waterbirths compared with land-births: an observational study ofnine years. J Perinat Med 2004;32:308-14.
16. Grodzka M, Makowska P, Wielgos M, Przybos A, Chrostowska J, Marianowski L. Water birth in the parturients' estimation. Ginekol Pol 2001;72:1025-30.
17. Lenstrup C, Schantz A, Berget A, Feder E, Roseno H, Hertel J. Warm tub bath during delivery. Acta Obstet Gynecol Scand 1987;66:709-12.
18. Lee SL, Liu CY, Lu YY, Gau ML. Efficacy of warm showers on labor pain and birth experiences during the first labor stage. J Obst Gynecol Neonat Nurs 2013;42:19-28.
19. Taavoni S, Abdolahian S, Haghani H. Effect of sacrum perineum heat therapy on active phase labor pain and client satisfaction: a randomized, controlled trial study. Pain Med 2013;14:1301-6.
20. Shirvani MA, Ganji J. The influence of cold pack on labour pain relief and birth outcomes: a randomised controlledtrial. J Clin Nurs 2014;23:2473-80.
21. Ganji Z, Shirvani MA, Rezaei-Abhari F, Danesh M. The effect of intermittent local heat and cold on labor pain and child birth outcome. Iran J Nurs Midwifery Res 2013;18:298-303.
22. Adams ED, Bianchi AL. A practical approach to labor support. J Obstet Gynecol Neonatal Nurs 2008;37:106-15.
23. Lane E, Latham T. Managing pain using heat and cold therapy: Elaine Lane and TracyLatham discuss the benefits of using non-pharmacological interventions to help improvechildren's experience of pain in hospital settings. Pediatr Nurs 2009;21:14-8.
24. Vermelis JM, Wassen MM, Fiddelers AA, Nijhuis JG, Marcus MA. Prevalence andpredictors of chronic pain after labor and delivery. Curr Opin Anesthesiol 2010;23:295-9.
26. Chaichian S, Akhlaghi A, Rousta F, Safavi M. Experience of water birth delivery in Iran. Arch Iran Med 2009;12: 468-71.
27. Mollamahmutoglu L, Moraloglu O, Ozyer S, Su FA, Karayalcin R, Hancerlioglu N, et al. The effects of immersion in water on labor, birth and newborn and comparison with epiduralanalgesia and conventional vaginal delivery. J Turk Ger Gynecol Assoc 2012;13:45.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 120-127

GYNAECOLOGY

Lidocaine Prilocaine Cream in Conjunction with Paracervical Block versus Placebo with Paracervical Block for Pain Relief during Fractional Curettage

Bordin Duangrudeesawat, M.D.*
Sukanya Srinil, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To study the efficacy of lidocaine prilocaine cream apply at cervix in conjunction with paracervical block versus placebo with paracervical block for pain reduction during fractional curettage.

Materials and Methods: One hundred and six women who underwent fractional curettage at Khon Kaen Hospital were enrolled in a randomized, double-blinded, placebo-controlled trial. The participants were randomly allocated into two groups, received lidocaine prilocaine cream plus paracervical block applied onto cervix (n = 53) versus placebo cream plus paracervical block (n = 53) before performing fractional curettage. Pain score was measured at tenaculum placement, during procedure, immediately after and 30 minutes after the procedure, using a 10 centimeters visual analog scale (VAS). The adverse events and additional analgesia were also recorded.

Results: Baseline characteristics were similar between groups. Mean pain score during fractional curettage in lidocaine prilocaine cream plus paracervical block was significantly lower than placebo cream plus paracervical block (2.80 ± 0.29, 95% confidence interval (CI) 2.21-3.38 vs. 5.34 ± 0.39, 95%CI 4.55-6.13, $p < 0.001$). Adverse events such as lightheadedness, palpitation and tinnitus were found without statistically significant difference between groups. None of the participants requested an additional analgesia.

Conclusion: Lidocaine prilocaine cream in conjunction with paracervical block had better pain relief during fractional curettage than in control group without serious adverse events.

Keywords: fractional curettage, lidocaine prilocaine cream, paracervical block, visual analog scale.

Correspondence to: *Bordin Duangrudeesawat, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand. Email: bordin.dear@gmail.com*

Received: 30 September 2020, **Revised:** 2 November 2020, **Accepted:** 6 January 2021

การศึกษาประสิทธิภาพของการทาครีมยาชาที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก เปรียบเทียบกับการทาครีมยาหลอกร่วมกับการฉีดยาชาข้างปากมดลูกในการลดความเจ็บปวดระหว่างการทำหัตถการขูดมดลูกแบบแยกส่วน

บดินทร์ ดวงฤดีสวัสดิ์, สุกัญญา ศรีนิล

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพของการทาครีมยาชาที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก เปรียบเทียบกับการทาครีมยาหลอกที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูกในการลดความเจ็บปวดระหว่างการขูดมดลูกแบบแยกส่วน*

วัสดุและวิธีการ*: สตรีที่มีข้อบ่งชี้ในการทำหัตถการขูดมดลูกแบบแยกส่วนที่เข้ารับการรักษาในโรงพยาบาลขอนแก่น จำนวน 106 คน ถูกสุ่มแบ่งเป็นสองกลุ่ม คือกลุ่มที่ได้รับการทาครีมยาชาที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก และกลุ่มที่ได้รับการทาครีมยาหลอกที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูกก่อนทำหัตถการขูดมดลูกแบบแยกส่วน สตรีทั้งสองกลุ่มได้รับการประเมินความเจ็บปวดโดยใช้มาตรวัดความเจ็บปวดด้วยสายตาจำนวน 4 ครั้ง คือ ขณะใช้อุปกรณ์ยึดจับปากมดลูก ระหว่างทำหัตถการขูดมดลูกแบบแยกส่วน หลังทำหัตถการขูดมดลูกแบบแยกส่วนเสร็จทันที และหลังทำหัตถการขูดมดลูกแบบแยกส่วนเสร็จนาน 30 นาที รวมถึงมีการประเมินภาวะแทรกซ้อนจากการใช้ยาและความต้องการยาแก้ปวดชนิดอื่นเพิ่มเติม*

ผลการศึกษา*: ข้อมูลลักษณะพื้นฐานทางประชากรศาสตร์ของทั้งสองกลุ่มไม่แตกต่างกัน คะแนนความเจ็บปวดระหว่างการทำหัตถการขูดมดลูกแบบแยกส่วนในกลุ่มที่ทาครีมยาชาที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก (กลุ่มทดลอง) น้อยกว่ากลุ่มที่ทาครีมยาหลอกที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก (กลุ่มควบคุม) อย่างมีนัยสำคัญทางสถิติ (ค่าเฉลี่ยคะแนนความเจ็บปวด ± ส่วนเบี่ยงเบนมาตรฐานของกลุ่มทดลอง และกลุ่มควบคุมมีค่า 2.80 ± 0.29, 5.34 ± 0.39 ตามลำดับ, $p < 0.001$) ภาวะแทรกซ้อนที่พบในทั้งสองกลุ่ม คือ วิงเวียนศีรษะ ใจสั่น และหูอื้อ ซึ่งพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ และเป็นภาวะแทรกซ้อนที่ไม่รุนแรง รวมถึงไม่มีการใช้ยาแก้ปวดชนิดอื่นเพิ่มเติมในทั้งสองกลุ่ม*

สรุป*: การทาครีมยาชาที่ปากมดลูกร่วมกับการฉีดยาชาข้างปากมดลูก สามารถลดความเจ็บปวดระหว่างทำหัตถการขูดมดลูกแบบแยกส่วนได้อย่างมีนัยสำคัญทางสถิติ และไม่พบภาวะแทรกซ้อนที่รุนแรงจากการใช้ยา*

คำสำคัญ*: การขูดมดลูกแบบแยกส่วน, ครีมยาชา, การฉีดยาชาข้างปากมดลูก, การให้คะแนนความเจ็บปวดโดยใช้มาตรวัดความเจ็บปวดด้วยสายตา*

Introduction

Fractional curettage is a common procedure for evaluating the causes of abnormal uterine bleeding[1]. In patients that have clinicals or risk factors that mimic endometrial cancer, fractional curettage is needed to investigate before treatment. In patients undergoing this operation in an outpatient setting, the requirement of an analgesic is inevitable. The various procedures during fractional curettage such as placement of the tenaculum for traction of the uterine cervix as well as the curettage itself can cause pain sensation. The analgesic efficacy of various pain-relief procedures has been tested for women undergoing fractional curettage. Although use of general anesthesia provides complete analgesia, it carries higher mortality and morbidity risk than properly administered local anesthetics[2].

The sensory innervation of the female pelvic organs derives from the superior hypogastric plexus or presacral nerve, pelvic nerves and ovarian plexus. Afferent fibers from the upper vagina, uterus, proximal segment of the fallopian tubes, bladder, urethra and rectum pass through the paracervical region and into the uterosacral folds and meet in the hypogastric plexus and pelvic nerves[3]. Paracervical block anesthetizes the second to fourth sacral nerve roots that innervate the cervix and the lower part of the uterine body[4]. The paracervical block is one of the most common procedures used for relief pain in patients undergoing fractional curettage[1], but the pain intensity under paracervical block is still moderate pain[5].

Five percent EMLA® cream is composed of two local anesthetics-lidocaine 25 mg/g and prilocaine 25 mg/g. When 5% EMLA® cream is applied to a mucous membrane, absorption is rapid, so occlusive dressings are not necessary. Ten minutes application time trended to produce the longest duration of analgesia of about 45 min[6,7]. One study reported the application of lidocaine prilocaine cream on the uterine cervix before hysterosalpingogram (HSG) relieved pain during the procedure. Cervical instrumentation was, moreover, the most painful step during the procedure and the use of lidocaine prilocaine cream decreased the pain during this step[8]. It has also been used locally on the uterine cervix before laser ablation and hysteroscopy and was found to reduce the patient's pain[9,10].

The objective of the current study was to evaluate the efficacy of lidocaine prilocaine cream versus placebo in conjunction with paracervical block for pain reduction during fractional curettage.

Materials and Methods

This study was a randomized, double-blinded, placebo-controlled trial. The study was reviewed and approved by Khon Kaen Hospital Institute Review Board for Human Research. All participants were informed about the study and signed informed consent before enrollment.

Between January 2020 and July 2020, we recruited 106 women with abnormal uterine bleeding indicated for fractional curettage at Khon Kaen Hospital. We excluded women with coagulopathy, currently using anticoagulant or antiplatelet drugs, having active liver or kidney disease, having lidocaine hypersensitivity, or being pregnant.

The participants were randomized to two groups using a computer-generated block of four: the study group – lidocaine prilocaine cream in conjunction with paracervical block, and the control group - placebo given in conjunction with paracervical block. The randomization list was kept in a sealed opaque envelope. The fractional curettage was performed by trained physicians not involved in the study. The physicians and assistant nurses were masked to the group assignments.

At first, the participants were in the lithotomy position. After twice rinsing the vagina and cervix with betadine, a paracervical block injection was done with a 23-gauge spinal needle at 3 and 9 o'clock of the cervicovaginal reflection at an estimated depth of 1 cm. Twenty milliliters of 1% lidocaine (without adrenaline) was given to each participant (10 ml at each site).

The study group and control group received 5 g of 5% lidocaine prilocaine cream and placebo, respectively. Due to the awareness of lidocaine toxicity, the maximum dose should not exceed 7 mg/kg. All participants in the study group were given a total 325

mg of lidocaine, which did not reach the toxic level. The 5% lidocaine prilocaine cream or placebo was applied to the cervix and external os using a cotton swab. After waiting 10 minutes, the fractional curettage was performed.

The fractional curettage was performed step-by-step, using a tenaculum grasped at 2 and 10 o'clock at anterior lip of the cervix. A curette number 00 was used for endocervical curettage. A uterine sound was inserted into uterine cavity to measure the uterine depth before performing endometrium curettage using a curette number 0.

The pain score was recorded using a 10-cm visual analog scale (VAS). Zero represented no pain and 10 represented the worst pain. The participants were asked by the assistant nurse to make a mark on the line that corresponded to their level of perceived pain intensity. Each participant was asked to evaluate pain assessment 4 times; at tenaculum placement, during endometrial curettage 15 s after beginning the procedure, immediately after the procedure, and 30 min after the procedure. All participants could ask for additional analgesia if/when needed.

Vital signs and adverse events i.e., lightheadedness, palpitation, numbness of lips, and tinnitus were recorded by a nurse until 2 h after the procedure. Additional analgesia was also recorded. The participants were appointed at three weeks later to inform about pathological report.

The primary outcome was the pain score during fractional curettage. The secondary outcomes were the pain score at the tenaculum placement immediate after and 30 min after the procedure, adverse effects, and the need for any additional analgesia. Baseline characteristics were recorded including age, body mass index (BMI), parity, prior curettage, post-menopausal status and indication for fractional curettage.

The sample size was calculated based on data from the pilot study with 80% power at the 5% level of significance with up to 10% dropout. The appropriate sample size was thus 106 participants (53 in each group). Data were analyzed using STATA version 13. Continuous variables were analyzed using the student t-test presented as means ± standard deviation (SD). Categorical variables were assessed using the chi-square or Fisher's exact test presented as percentages. A p value < 0.05 was considered statistically significant.

Results

During the study, there were 106 women who were indicated for fractional curettage at Khon Kaen Hospital. All of the participants were recruited into the study and randomly allocated into two groups the study group (lidocaine prilocaine cream in conjunction with paracervical block) (n = 53), and the control group (a placebo given in conjunction with paracervical block) (n = 53). There were no dropouts during the study, so the data from 106 women were analyzed (Fig. 1).

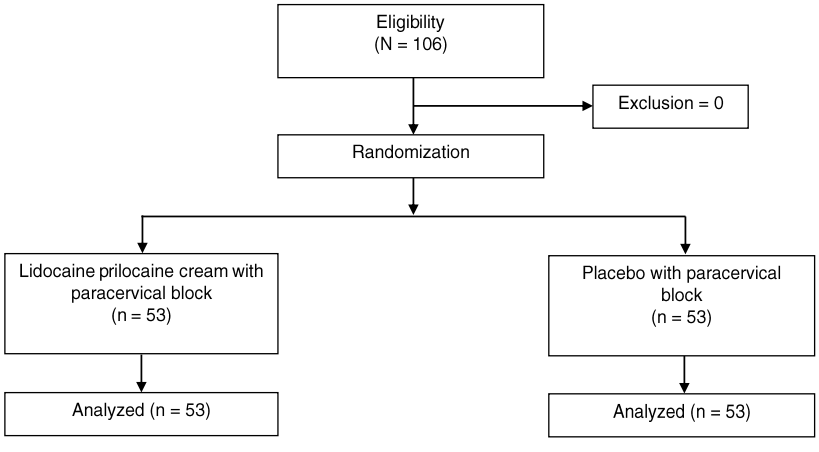


Fig. 1. Study flow diagram.

Both groups had similar baseline characteristics including age, BMI, parity, history of prior curettage, post-menopausal status, and indication for fractional curettage (Table 1).

The primary and secondary outcomes are presented in Table 2. The respective mean pain score was lower in the study vs. the placebo group during fractional curettage (2.80 ± 0.29, 95% confidence interval (CI) 2.21 - 3.38 vs. 5.34 ± 0.39, 95%CI 4.55 - 6.13, p < 0.001); at tenaculum placement (1.45 ± 0.26, 95%CI 0.93 - 1.97 vs. 2.35 ± 0.34, 95%CI 1.66 - 3.04, p = 0.04); and, immediately after treatment (2.91 ± 0.34, 95%CI 2.22 - 3.60 vs. 4.21 ± 0.38, 95%CI 3.44 to 4.98, p = 0.01). The pain score at 30 min was not significantly different between the groups (1.25 ± 0.18, 95%CI 0.89 - 1.60 vs. 1.66 ± 0.29, 95%CI 1.09 - 2.23, p = 0.22).

Table 1. Demographics and characteristics of the cases.

	Lidocaine prilocaine cream with paracervical block (n = 53)	Placebo with paracervical block (n = 53)	p value
Age (years), mean ± SD	49.70 ± 10.58	47.51 ± 8.89	0.25[c]
BMI (kg/m^2), mean ± SD	26.73 ± 4.77	25.12 ± 4.31	0.07[c]
Parity, n (%)			0.18[a]
Nullipara	3 (5.7)	7 (13.2)	
Multipara	50 (94.3)	46 (86.8)	
Prior curettage, n (%)	15 (28.3)	14 (26.4)	0.83[a]
Post-menopausal status, n (%)	17 (32.1)	10 (18.9)	0.12[a]
Indication, n (%)			0.26[b]
Abnormal uterine bleeding	36 (67.9)	39 (73.6)	
Postmenopausal bleeding	14 (26.4)	10 (18.9)	
Endometrial hyperplasia	3 (5.7)	4 (7.5)	
Other	0 (0.0)	0 (0.0)	

[a] chi-square test, [b] Fisher's exact test, [c] student t-test. SD: standard deviation, BMI: body mass index

Table 2. Primary and secondary outcomes.

VAS	Lidocaine prilocaine cream with paracervical block (n = 53)	Placebo with paracervical block (n = 53)	Mean different	95%CI	p value
At tenaculum placement					
mean ± SD	1.45 ± 0.26	2.35 ± 0.34	- 0.90	- 1.75 to - 0.05	0.04[c]
(95%CI)	(0.93 to 1.97)	(1.66 to 3.04)			
During fractional curettage					
mean ± SD	2.80 ± 0.29	5.34 ± 0.39	- 2.55	- 3.52 to - 1.57	< 0.001[c]
(95%CI)	(2.21 to 3.38)	(4.55 to 6.13)			
Immediate after procedure					
mean ± SD	2.91 ± 0.34	4.21 ± 0.38	- 1.30	- 2.31 to - 0.28	0.01[c]
(95%CI)	(2.22 to 3.60)	(3.44 to 4.98)			
Thirty minutes after procedure					
mean ± SD	1.25 ± 0.18	1.66 ± 0.29	- 0.41	- 1.08 to 0.25	0.22[c]
(95%CI)	(0.89 to 1.60)	(1.09 to 2.23)			

[c] student t-test, Significant p < 0.05. VAS: Visual analog scale, CI: confidence interval, SD: standard deviation

Adverse events such as lightheadedness, palpitation, and tinnitus were found in both groups (no significant difference), and none of the participants requested medical treatment or additional analgesia (Table 3).

The pathological report revealed benign endometrial tissue 88.68% (n = 94), endometrial hyperplasia with/without atypia 4.72% (n = 5), malignancy 3.77% (n = 4) and no endometrial tissue obtained 2.83% (n = 3)

Table 3. Adverse events and additional analgesia.

	Lidocaine prilocaine cream with paracervical block (n = 53)	Placebo with paracervical block (n = 53)	p value
Adverse events, n (%)			0.72
Lightheadedness	9 (17.0)	14 (26.4)	0.24[a]
Palpitation	5 (9.4)	5 (9.4)	1.00[a]
Numbness of lips	0 (0.0)	2 (3.8)	0.50[b]
Tinnitus	7 (13.2)	9 (17.0)	0.59[a]
Hypotensive event	0 (0.0)	0 (0.0)	NA
Additional analgesic, n (%)	0 (0.0)	0 (0.0)	NA

[a] chi-square test, [b] Fisher's exact test.

Discussion

Use of lidocaine prilocaine cream in conjunction with paracervical block resulted in a significantly lower pain score than placebo used in conjunction with paracervical block. On the basis that the lower part of uterine body and cervix is innervated by Frankenhauser's plexus (sacral plexus 2 - 4). Paracervical block should thus block not only uterine pain but also cervical pain. Notwithstanding, Thongrong et al[5], demonstrated that although paracervical block alone reduced pain during endometrial curettage, moderate pain persisted. The present study showed that the combination of lidocaine prilocaine cream in conjunction with paracervical block had a synergistic effect for pain reduction during fractional curettage, because lidocaine prilocaine cream anesthetizes the cervix which is innervated by Frankenhauser's plexus which uses the same pathway as the uterine body. The use of lidocaine prilocaine cream in conjunction with paracervical block could help patients to be more comfortable than using paracervical block alone.

Although there has been no study about the efficacy of lidocaine prilocaine cream for the pain reduction during fractional curettage, previous studies on cervical and uterine interventions provide relevant comparisons. Liberty et al[8], reported that the effect of applying lidocaine prilocaine cream on the uterine cervix for pain relief after performing HSG on 84 women who underwent HSG as part of an infertility evaluation. The study found that cervical instrumentation in the lidocaine prilocaine-treated patients was associated with significantly less pain than the placebo (3.3 ± 2.9 vs. 4.9 ± 2.7, p = 0.02).

Tavakolian et al[11], reported on the effect of lidocaine prilocaine cream on the uterine cervix to determine intrauterine device (IUD) insertion pain among 92 women who underwent IUD insertion. The study demonstrated that lidocaine prilocaine cream significantly reduced pain during the use of a tenaculum compared with a placebo (1.52 ± 1.85 vs. 4.30 ± 2.40, p < 0.001). In addition, the mean pain score during insertion of a hysterometer in the lidocaine prilocaine cream group was associated with significantly less pain than the placebo group (3.11 ± 2.53 vs. 5.20 ± 2.31, p < 0.001). The results of two previous studies agreed with our study and indicated that lidocaine prilocaine cream in conjunction with paracervical block significantly reduced the pain score over against placebo in conjunction

with paracervical block.

Besides the primary outcome, we found that the pain score at tenaculum placement and immediately after fractional curettage was significantly lower in the study group (lidocaine prilocaine cream in conjunction with paracervical block) over against the control group (placebo given in conjunction with paracervical block). Lidocaine prilocaine cream produced the longest duration of analgesia (about 45 min) and reduced pain scores (i.e., 30 min after fractional curettage). The pain score 30 min after the procedure was not significantly between groups as mild intensity pain persisted in both groups.

None of the participants requested any additional analgesia. There was no significant difference in adverse events (whether lightheadedness, palpitation, numbness of lips, or tinnitus) between the two groups. These adverse events were mild and resolved within a few minutes without medical treatment. Zilbert[12] reviewed the effect of using lidocaine prilocaine cream for pain relief during minor gynecological procedures and found that it was well-tolerated and adverse reactions were generally mild, local, and transient.

Although the standard procedure for diagnosis of women with abnormal uterine bleeding is endometrial sampling, fractional curettage remains an alternative. Fractional curettage can be obtained from the endocervix and/or the entire of endometrial tissue useful for both diagnosis and therapy, particularly in cases of active uterine bleeding. Fractional curettage under paracervical block can be performed in a minor operative setting without hospital admission. Based on the literature review, fractional curettage causes moderate pain, so our findings have practical implications for reducing pain during such procedures.

The strengths of this study were that it was (a) a randomized, double-blinded, placebo-controlled trial, (b) no patients dropped out, and (c) all participants did their own pain assessment. The limitation was the lack of patients, who are having the difficulty of fractional curettage such as cervical stenosis. Therefore, the study of lidocaine prilocaine cream in conjunction with paracervical block for pain relief in this group of patients may be needed.

Conclusion

Compared with placebo, lidocaine prilocaine cream in conjunction with paracervical block significantly reduced pain during fractional curettage.

Acknowledgements

The authors would like to thank (a) staff at the Department of Obstetrics and Gynecology, Khon Kaen Hospital for their assistance and support; (b) all the participants for their co-operation; and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Api O, Ergen B, Api M, Ugurel V, Emeksiz MB, Unal O. Comparison of oral nonsteroidal analgesic and intrauterine local anesthetic for pain relief in uterine fractional curettage: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 2010;203:28.e1-7.
2. Arora A, Shukla A, Saha SC. Effectiveness of intrauterine lignocaine in addition to paracervical block for pain relief during dilatation and curettage, and fractional curettage. J Obstet Gynaecol India 2016;66:174-9.
3. Arnau B, Jovell E, Redón S, Canals M, Mir V, Jiménez E. Lidocaine-prilocaine (EMLA®) cream as analgesia in hysteroscopy practice: a prospective, randomized, non-blinded, controlled study. Acta Obstet Gynecol Scand 2013;92:978-81.
4. Tangsiriwatthana T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Paracervical local anaesthesia for cervical dilatation and uterine intervention. Cochrane Database Syst Rev 2013:9:CD005056.
5. Thongrong P, Jarruwale P, Panichkul P. Effectiveness of paracervical block versus intravenous morphine during uterine curettage: a randomized controlled trial. J Med Assoc Thai 2011;94:403-7.
6. Ljunghall K, Lillieborg S. Local anaesthesia with a lidocaine/prilocaine cream (EMLA) for cautery of condylomata acuminata on the vulval mucosa. The effect of timing of application of the cream. Acta Derm Venereol 1989;69:362-5.
7. Van der Burght M, Schønemann N, Laursen J, Arendt-Nielsen L, Bjerring P. Duration of analgesia following application of eutectic mixture of local anaesthetics (EMLA) on genital mucosa. Acta Derm Venereol

1993;73:456.
8. Liberty G, Gal M, Halevy-Shalem T, Michaelson-Cohen R, Galoyan N, Hyman J, et al. Lidocaine–Prilocaine (EMLA) cream as analgesia for hysterosalpingography: a prospective, randomized, controlled, double blinded study. Hum Reprod 2007;22:1335-9.
9. Zilbert A. Topical anesthesia for minor gynecological procedures: a review. Obstet Gynecol Surv 2002;57: 171-8.
10. Zullo F, Pellicano M, Stigliano C, Di CC, Fabrizio A, Nappi C. Topical anesthesia for office hysteroscopy. A prospective, randomized study comparing two modalities. J Reprod Med 1999;44:865-9.
11. Tavakolian S, Doulabi MA, Baghban AA, Mortazavi A, Ghorbani M. Lidocaine-prilocaine cream as analgesia for IUD insertion: a prospective, randomized, controlled, triple blinded study. Glob J Health Sci 2015;7:399.
12. Zilbert A. Topical anesthesia for minor gynecological procedures: a review. Obstet Gynecol Surv 2002;57: 171-8.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 128-135

GYNAECOLOGY

Quality of Life after Treatment by Vaginal Pessary versus Surgery in Symptomatic Pelvic Organ Prolapsed Thai Patients

Supakit Panjapong, M.D.*,
Pranom Buppasiri, M.D.*,
Chompilas Chongsomchai, M.D.*,
Teerayut Temtanakitpaisan, M.D.*

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

ABSTRACT

Objectives: To compare the change in quality of life of Thai patients with symptomatic pelvic organ prolapse treated with vaginal pessary or surgery using validated prolapse quality of life (P-QOL) questionnaire.

Materials and Methods: The study recruited patients in one by one stratified simple random sampling in the same prolapse stages of forty patients in the pessary group and forty patients in the surgery group from the urogynecology clinic between January 2018 and August 2019. The data were collected using the P-QOL questionnaire before the treatment and 3 months and 6 months after the treatment.

Results: The mean age was 65.7 ± 7.7 years and body mass index was 24.9 ± 3.7 kg/m^2. After treatment with either pessary or surgery, almost all P-QOL domains significantly improved at 3 months and 6 months except in the personal relationships and sleep/energy domains in the pessary group in which the domains were not different from the baseline. General health perceptions and sleep/energy domains significantly improved more in the surgery group at 3 months ($p = 0.01$ and $p = 0.023$) and 6 months ($p = 0.024$ and $p = 0.007$,) after treatment. The mean ± standard deviation of satisfaction scores after treatment in pessary and surgery at 3 months (8.9 ± 1.4 and 9.3 ± 1.0 ($p = 0.509$), and 6 months (9.4 ± 1.2 and 9.3 ± 1.1 ($p = 1.000$) were not statistically different.

Conclusion: The quality of life in symptomatic prolapse after treatment with vaginal pessary or surgery improved. The majority of patients were very satisfied with the outcomes of either treatment.

Keywords: pelvic organ prolapse, pessary, quality of life, surgery.

Correspondence to: *Teerayut Temtanakitpaisan, M.D., Department of Obstetrics and gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. E-mail: jacktemtanakitpaisan@hotmail.com*

Received: 30 September 2020, **Revised:** 14 December 2020, **Accepted:** 29 December 2020

คุณภาพชีวิตหลังได้รับการรักษาด้วยอุปกรณ์พยุงช่องคลอดเปรียบเทียบกับการผ่าตัดในผู้ป่วยไทยที่มีอุ้งเชิงกรานหย่อน

ศุภกิตต์ ปัญจพงษ์, ประนอม บุพศิริ, โฉมพิลาศ จงสมชัย, ธีระยุทธ เต็มธนะกิจไพศาล

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบคุณภาพชีวิตที่เปลี่ยนแปลงในผู้ป่วยไทยที่มีภาวะอุ้งเชิงกรานหย่อนหลังได้รับการรักษาด้วยอุปกรณ์พยุงช่องคลอดกับการผ่าตัดโดยใช้แบบสอบถามคุณภาพชีวิต P-QOL ฉบับภาษาไทย*

วัสดุและวิธีการ: *สุ่มตัวอย่างแบบชั้นภูมิเปรียบเทียบผู้ป่วยที่มีระดับอุ้งเชิงกรานหย่อนระดับเดียวกัน ได้รับรักษาโดยใช้อุปกรณ์พยุงทางช่องคลอด หรือผ่าตัด กลุ่มละ 40 คน จากคลินิกนรีเวชทางเดินปัสสาวะระหว่างเดือนมกราคม 2561 ถึงสิงหาคม 2562 ด้วยแบบสอบถามคุณภาพชีวิต P-QOL ฉบับภาษาไทย ทั้งก่อนรับการรักษา และหลังการรักษาที่ 3 เดือน และ 6 เดือน*

ผลการศึกษา: *อายุเฉลี่ยและน้ำหนักเฉลี่ยของผู้ป่วยส่วนใหญ่อยู่ที่ 65.7 ± 7.7 ปี และ 24.9 ± 3.7 กิโลกรัม/เมตร^2 หลังรับการทั้งสองกลุ่มมีคุณภาพชีวิต (P-QOL) ดีขึ้นอย่างมีนัยสำคัญทั้งใน 3 เดือนและ 6 เดือน ยกเว้นหมวดความสัมพันธ์ส่วนบุคคลและหมวดคุณภาพชีวิตการนอน/พลังในการทำงาน หลังรับการผ่าตัดเมื่อเทียบกับการใส่อุปกรณ์พยุงช่องคลอด คุณภาพชีวิตในหมวดสุขภาพทั่วไปและหมวดคุณภาพชีวิตการนอน/พลังในการทำงานดีขึ้นอย่างมีนัยสำคัญทั้งใน 3 เดือน (p = 0.01 และ 0.023 ตามลำดับ) และ 6 เดือน (p = 0.024 และ 0.007 ตามลำดับ) ค่าเฉลี่ยความพึงพอใจหลังรับการรักษาด้วยอุปกรณ์พยุงช่องคลอด และการผ่าตัดที่ 3 เดือน (8.9 ± 1.4 และ 9.3 ± 1.0 (p = 0.509)) และ 6 เดือน (9.4 ± 1.2 และ 9.3 ± 1.1 (p = 1.000)) ไม่พบความแตกต่างอย่างมีนัยสำคัญ*

สรุป: *หลังการรักษาผู้ป่วยที่มีภาวะอุ้งเชิงกรานหย่อนด้วยอุปกรณ์พยุงช่องคลอดหรือได้รับการผ่าตัดพบว่ามีคุณภาพชีวิตดีขึ้น และมีความพึงพอใจอย่างมากหลังการรักษาทั้งสองกลุ่ม*

คำสำคัญ: *ภาวะอุ้งเชิงกรานหย่อน, อุปกรณ์พยุงช่องคลอด, คุณภาพชีวิต, การผ่าตัด*

Introduction

Pelvic organ prolapse (POP) is the downward descent of one or more compartments of vagina and uterus into vagina or protruding through the hymen[1]. It is a benign condition probably leading to vaginal bulge, pelvic pressure, voiding dysfunction, defecatory dysfunction and sexual dysfunction[1]. A negative impact on quality of life (QoL) may be attributed to these symptomatic prolapses[2]. The risk factors accounting for the development of POP are age, parity, vaginal delivery, obesity, connective tissue diseases, chronic constipation and menopausal status.

In addition to lifestyle modifications, a vaginal pessary is a non-surgical option to relieve the POP symptoms and is considered to be the first offer rather than surgery[3]. Nevertheless, the prolapse surgery is essentially required to correct all affected vaginal compartments to restore the vaginal anatomy with operation techniques that primarily rely on the physicians' discretion and expertise[1].

Although POP surgery has considerable advantages over pessary use, the risk of complications after surgery and the cost-effectiveness are required to be taken into account[4].

Given the improvement of the symptoms after treatment with either treatment, however, two prospective studies showed similar improvement in prolapse, urinary, bowel symptoms, sexual function as well as the QoL[3,5].

As for the cultural differences, to the knowledge of present investigators, few studies have compared the outcomes of both treatments among Thai women. The aim of the study was, therefore, to evaluate and compare the changes in QoL of Thai women with symptomatic POP who were treated with vaginal pessaries and surgery after 3 and 6 months, in which the validated prolapse quality of life (P-QOL) questionnaire and satisfaction scores were used to collect data.

Materials and methods

This was a quasi-experimental study that pelvic organ prolapsed patients selected the treatment by pessary or surgery depending on their preference and co-morbidities. The study protocol was approved by the Human Research Ethics Committee, Khon Kaen University (HE621008). After obtaining a written informed consent from each participant, data collection began from the participants attending an urogynecology clinic at the tertiary hospital between January 2018 and August 2019. As for the inclusion criteria, the participants were required to be 18 years of age or over, have developed prolapse stage II or more (POP-Q system), and were to have been treated with either vaginal pessary or surgery. Patients illiterate in Thai language and who did not follow-up for 6 months were excluded from the study. Patients who changed the treatment from pessary to surgery were considered as a failed pessary and the P-QOL scores were not evaluated. The pelvic organ prolapsed patients selected the treatment using their own discretion after the physicians gave them the information regarding treatment options. For care of the pessaries, patients were advised, if possible, to remove and clean every night. Once a week, however, was considered acceptable. Participants were enrolled with one by one stratified simple random sampling in the same prolapse stage. In cases who could not follow-up in person were contacted by phone.

The validated P-QOL questionnaire in Thai version[6] was administered before treatment and 3 months and 6 months after treatment. A lower score indicates better quality of life; meanwhile, a higher score indicates detrimental effects on quality of life. Moreover, the satisfaction with the treatments using the visual analog scale at 3 months and 6 months after treatment, were also investigated.

According to the pilot study, the mean difference ± standard deviation (SD) of P-QOL after the treatment with pessary was 23.50 ± 31.68 and 36.8 ± 42.85 in surgery. It was assumed that there were at least 25 points of mean differences in the treatment group. In order to achieve a power of 80% and a level of significance of 5%, 40 patients per treatment were required.

Statistical analysis was performed using STATA/SE version 10.1, and a test of normality was conducted

using Kolmogorov-Smirnov testing. The collected data were presented as percentages, means, and medians. The student's t-test, chi-square, Fisher's exact and Mann-Whitney U tests were used to assess the appropriateness to compare between pessary and surgical groups. A generalized estimating equation (GEE) was used to compare the mean difference of QoL scores between two groups. A p value of < 0.05 was considered statistically significant.

Results

One hundred eighteen patients were recruited, seventy-five were in the pessary group and forty-three patients were in the surgery group. Patients were enrolled by stratified simple random sampling in the same prolapse stage. Forty of them were assigned in the pessary group (50%) and forty in surgery group (50%). The data were collected during the follow-up period. In case of loss of in-person contact follow-up (46.3%) (15 patients in pessary group and 22 patients in surgery group), they were all contacted by phone. Thirty-nine patients (97.5%) in the pessary group were fitted with support pessaries, while only one (2.5%) was fitted with space occupying pessary (Donut pessary). There were two surgical routes to restore pelvic floor anatomy in this study depending on physician experience and preference; a vaginal approach in 31 patients (77.5%) which was vaginal hysterectomy with sacrospinous ligament fixation with anterior and posterior colporrhaphy and the laparoscopic approach in 9 patients (22.5%). Six patients underwent laparoscopic sacrocolpopexy; 5 cases had vaginal vault prolapse and another one case was prolapsed with a paravaginal defect. Three patients had undergone laparoscopic high uterosacral ligament suspension. In cases who had the uterus in situ, they had laparoscopic hysterectomy performed as an additional procedure.

The mean age ± SD was 65.7 ± 7.7 years and their mean body mass index (BMI) ± SD was 24.9 ± 3.7 kg/m^2 and menopausal status was 96.3%. There was no statistical difference between the pessary and surgery groups in respect of age, BMI, occupation, marital status, parity, menopausal status and POP-Q stage (Table 1). For the underlying diseases, 5 patients suffered from ischemic heart disease and all of them were in the pessary group ($p = 0.021$). No one in the pessary group changed to the surgery group.

Table 1. Patient baseline characteristics (n = 80).

Variables	Pessary group (n = 40)	Surgery group (n = 40)	Total	p value
1. Age (years), mean ± SD	67.25 ± 7.48	64.23 ± 7.61	65.74 ± 7.65	0.077
2. BMI (kg/m^2), mean ± SD	24.11 ± 3.86	25.61 ± 3.42	24.86 ± 3.70	0.071
3. Occupation, n = yes (%)				0.23
3.1 Agricultural workers	19 (47.5)	10 (10)	29 (36.25)	
3.2 Self-employed	6 (15)	13 (32.5)	19 (23.75)	
3.3 Trader	7 (17.5)	6 (15)	13 (16.25)	0.83[a]
3.4 Office worker	1 (2.5)	1 (2.5)	2 (2.5)	0.12[a]
3.5 Civil servant	3 (7.5)	6 (15)	9 (11.25)	0.26[b]
3.6 None	4 (10)	4 (10)	8 (10)	
4. Marital status, n = yes (%)				0.79
4.1 Single	0	0	0	
4.2 Married	29 (72.5)	32 (80)	68 (85)	
4.3 Divorced	1 (2.5)	1 (2.5)	2 (2.5)	
4.4 Widowed	10 (25)	7 (17.5)	17 (21.25)	
5. Parity, mean ± SD	3.43 ± 1.26	3.25 ± 1.45	3.34 ± 1.35	0.565
6. Menopause, n (%)	39 (97.5)	38 (95)	77 (96.25)	0.999
7. History of vaginal birth, n (%)	38 (95)	36 (90)	74 (92.50)	0.675

Table 1. Patient baseline characteristics (n = 80). (Cont.)

Variables	Pessary group (n = 40)	Surgery group (n = 40)	Total	p value
8. Underlying disease, n (%)	21 (52.5)	27 (67.5)	48 (60)	0.171
8.1 Hypertension	15 (37.5)	20 (50)	35 (43.75)	0.260
8.2 Diabetes mellitus	10 (25)	9 (22.5)	19 (23.75)	0.793
8.3 Dyslipidemia	5 (12.5)	10 (25)	15 (18.75)	0.152
8.4 SLE	0	1 (2.5)	1 (1.25)	0.314
8.5 Ischemic heart disease	5 (12.5)	0	5 (6.25)	0.021
8.6 CKD	0	1 (2.5)	1 (1.25)	0.314
8.7 GERD	0	1 (2.5)	1 (1.25)	0.314
8.8 Gout	0	1 (2.5)	1 (1.25)	0.314
8.9 Osteoarthritis of knee	0	1 (2.5)	1 (1.25)	0.314
8.10 Spinal stenosis	1 (2.5)	0	1 (1.25)	0.314
8.11 Hyper/hypothyroid	2 (5)	1 (2.5)	3 (3.75)	0.556
8.12 Breast cancer	0	1 (2.5)	1 (1.25)	0.314
9. History of hysterectomy, n (%)	4 (10)	5 (12.50)	9 (11.39)	1.000
10. Overall stage of pelvic organ prolapse Quantification system (POP-Q), n (%)				
Stage II	12 (30)	12 (30)	24 (30)	1.000
Stage III	21 (52.5)	21 (52.5)	42 (52.50)	1.000
Stage IV	7 (17.5)	7 (17.5)	14 (17.50)	1.000

SD: standard deviation, BMI: body mass index, SLE: systemic lupus erythematosus, CKD: chronic kidney disease, GERD: gastroesophageal reflux disease

The P-QOL scores at baseline before treatment in each group are shown in Table 2. The patients with symptomatic prolapse were affected adversely by the disease, including general health perceptions, impacts of prolapse, role limitations, physical limitations, emotions and severity measures which were not different at the baseline between two groups. In the sleep/energy domain, patients in the surgery group significantly suffered more than the pessary group (p = 0.023). After treatment with either pessary or surgery, all P-QOL domains significantly improved at 3 months and 6 months except for personal relationships and sleep/energy domains in the pessary group.

Table 2. Patient quality of life score before treatment between pessary and surgery groups (n = 80).

P-QOL domain	Baseline of pessary median (IQR)	Baseline of surgery median (IQR)	p value
1. General health perceptions	50 (25, 75)	50 (50, 75)	0.095
2. Prolapse impact	67 (67, 100)	67 (33, 100)	0.556
3. Role limitations	33 (0, 67)	33 (17, 67)	0.477
4. Physical limitations	17 (0, 58.5)	33 (17, 91.5)	0.055
5. Social limitation	0 (0, 27.5)	5.5 (0, 44)	0.241
6. Personal relationships	0 (0, 0)	0 (0, 0)	0.477
7. Emotions	44 (22, 67)	33 (11, 56)	0.586
8. sleep/energy	0 (0, 0)	0 (0, 50)	0.023
9. Severity measures	33 (17, 37.5)	25 (12.5, 37.5)	0.763
10. Total score	28.5 (19.5, 39)	31.5 (25, 51)	0.202

P-QOL: Validation of the prolapse quality of life questionnaire, IQR: Interquartile range

When comparing the two groups, general health perceptions and sleep/energy domains significantly improved more in the surgery group at 3 months (p = 0.01 and p = 0.023) and 6 months (p = 0.024 and p = 0.007) after treatment (Table 3).

After treatment with either pessary or surgery, vaginal bulging, urinary frequency, urinary urgency and voiding difficulty improved significantly. The improvement of urgency urinary incontinence symptoms was observed solely in the surgery group (p = 0.025); however, after both pessary and surgical treatment, neither stress urinary incontinence nor constipation improved. The improvement of symptoms in relation to the symptoms of pelvic organ prolapse were not statistically different at 6 months after treatment in both pessary and surgery groups (Table 4).

Table 3. Comparison of P-QOL domain score between pessary and surgery groups (n = 80).

Domains	3 months after treatment					6 months after treatment				
	Pessary		Surgery		difference between group (p value)	Pessary		Surgery		difference between group (p value)
	mean change from baseline	p value	mean change from baseline	p value		mean change from baseline	p value	mean change from baseline	p value	
1. General health perceptions	- 14.38	0.001	- 31.23	0.001	- 16.85 (0.010)	- 15	< 0.001	- 30	< 0.001	- 15 (0.024)
2. Prolapse impact	- 53.47	< 0.001	- 59.23	< 0.001	- 5.77 (0.922)	- 63.47	< 0.001	- 60.90	< 0.001	2.57 (1.000)
3. Role limitations	- 37.48	< 0.001	- 40.84	< 0.001	- 3.37 (1.000)	- 36.64	< 0.001	- 42.93	< 0.001	- 6.28 (0.816)
4. Physical limitations	- 29.62	< 0.001	- 42.16	< 0.001	- 12.54 (0.256)	- 27.95	< 0.001	- 42.58	< 0.001	- 14.63 (0.154)
5. Social limitations	- 14.96	< 0.001	- 21.06	< 0.001	- 6.10 (0.624)	- 14.68	< 0.001	- 21.62	< 0.001	- 6.94 (0.501)
6. Personal relationships	- 4.55	0.229	- 6.67	0.021	- 2.12 (1.000)	- 3.72	0.482	- 6.25	0.036	- 2.53 (1.000)
7. Emotions	- 34.92	< 0.001	- 35.51	< 0.001	- 0.59 (1.000)	- 37.42	< 0.001	- 37.18	< 0.001	0.24 (1.000)
8. Sleep/ energy	- 6.68	0.147	- 20.41	< 0.001	- 13.73 (0.023)	- 4.18	0.765	- 19.99	< 0.001	- 15.81 (0.007)
9. Severity measures	- 20.15	< 0.001	- 25.93	< 0.001	- 5.78 (0.324)	- 23.90	< 0.001	- 26.56	< 0.001	- 2.66 (1.000)
10. Total	- 23.96	< 0.001	- 31.49	< 0.001	- 7.53 (0.116)	- 25.16	< 0.001	32.04	< 0.001	- 6.88 (0.166)

P-QOL: Validation of the prolapse quality of life questionnaire

Table 4. The changes of pelvic organ prolapse related symptoms between pessary and surgery groups.

Symptoms	Pessary			Surgery			p value between two groups at 6 months
	Baseline n (%)	6 months n (%)	p value	Baseline n (%)	6 months n (%)	p value	
1. Vaginal bulge or lump	37 (92.5)	7 (17.5)	< 0.001	35 (87.5)	4 (10)	< 0.001	0.330
2. Frequency of urination	20 (50)	8 (20)	0.006	30 (75)	5 (12.5)	< 0.001	0.363
3. Urgency	21 (52.5)	12 (30)	0.045	21 (52.5)	8 (20)	0.002	0.302
4. Urgency urinary incontinence	16 (40)	14 (35)	1.000	20 (50)	9 (22.5)	0.025	0.217
5. Stress urinary incontinence	15 (37.5)	17 (42.5)	1.000	17 (42.5)	9 (22.5)	0.071	0.056
6. Voiding dysfunction	18 (45)	2 (5)	< 0.001	20 (50)	1 (2.5)	< 0.001	1.000
7. Constipation	14 (35)	10 (25)	0.529	19 (47.5)	11 (27.5)	0.072	0.799

The mean ± SD of satisfaction score (0-10) after treatment in pessary and surgery groups at 3 months (8.9 ± 1.4 and 9.3 ± 1.0 (p = 0.509), and 6 months (9.4 ± 1.2 and 9.3 ± 1.1 (p = 1.000) were not statistically different.

At the six-month follow-up, abnormal vaginal discharge was detected in one case and frequent pessary expulsion was observed in three cases. One

case was reported to have pelvic pain after laparoscopic surgery.

Discussion

This study compared the QoL of Thai patients with symptomatic POP who were treated with pessary and with surgery. It was found that both treatments significantly improved in almost all domains of the P-QOL questionnaire. Numerous studies have claimed that the QoL in pelvic organ prolapsed patients significantly improved after pessary[7-10] and surgery[11,12] treatments. These current study findings were consistent with those by Abdool et al[13] and by Lone et al studies[5], who employed both the Sheffield questionnaire and the validated International Consultation on Incontinence Questionnaire Vaginal Symptoms Module (ICIQ-VS) and the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI (SF)) questionnaires and found that the QoL after both treatments (pessary and surgery) significantly improved. In addition, considering each domain, this current study found personal relationships in the pessary group did not significantly improve from the baseline, similar to the report of Lone et al and Abdool et al.[5,13] The possible explanation might be because the patients with pessary use are required to remove the pessary regularly during night time to prevent complications; consequently, prolapse may protrude during the night and may interfere with sexual activity. Moreover, the current study revealed that the sleep/energy domains did not improve in the pessary group. This may be due to prolapse-related symptoms during removal of pessary such as the symptoms of urinary urgency or incomplete emptying that can cause urinary frequency during nighttime, which may cause sleep disturbance. In contrast, in the surgery group, according to the P-QOL questionnaire, all domains improved significantly. Therefore, surgery has more advantages over pessary in this aspect.

As for the changes of prolapse symptoms, it was found that stress urinary incontinence did not improve after pessary or surgery, and urgency urinary incontinence did not improve after pessary use but significantly improved after surgery. Moreover, the improvement of prolapse symptoms such as vaginal bulging, urinary frequency, urinary urgency and voiding difficulty significantly improved after both treatments. Such improvement could be due to relief of obstructive symptoms. These findings corresponded to the Abdool et al study[13].

The satisfaction scores in pessary and surgery at 3 months and 6 months after treatment were high, but there was no statistical difference between two groups. In contrast to the study from Peking University[14], in which the satisfaction score was relatively higher in surgery than the pessary group (4.9 ± 0.4 and 4.0 ± 1.3 scores, $p < 0.01$). The differences in the satisfaction scores may be because Chinese people have higher expectations. The pessary was used solely to support the pelvic organ rather than cure; thus, the satisfaction score was lower than that of surgery.

Patients' preference influences a selection of treatment[13]. One study from the Netherlands[15] reported that 48% of patients with POP symptoms preferred surgery, 36% preferred pessary and 16% preferred neither. Therefore, in addition to the treatment options and complications, the data on the QoL particularly in the same cultures are of importance in the counseling process to guide patients' decisions.

The current study had some limitations since the study was conducted as a quasi-experiment and did not randomize the patients due to patient preferences, co-morbidities and the course of follow-up was short. Patients were enrolled by determining the number of patients in the same stage and the baseline characteristics between two groups were similar; thus, the scores of the QoL were not unduly affected by the study; all ischemic heart disease (IHD) patients who ultimately selected pessary use after the physician gave them advice with the consideration of the underlying disease, then did so. This enrolment reflected the daily practice in the real setting, which was a strength of the current study.

According to the P-QOL questionnaire, the QoL

in symptomatic prolapse after treatment with vaginal pessary or surgery improved. The majority of prolapse patients were very satisfied with the outcomes of either treatment.

Acknowledgements

The authors would like to thank Professor James Arthur Will for editing the manuscript via the Publication Clinic KKU, Thailand.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Committee on Practice Bulletins-Gynecology and American Urogynecologic Society. Pelvic organ prolapse. Female Pelvic Med Reconstr Surg 2017; 23:353-64.
2. Digesu GA, Chaliha C, Salvatore S, Hutchings A, Khullar V. The relationship of vaginal prolapse severity to symptoms and quality of life. BJOG 2005;112:971-6.
3. Bodner-Adler B, Bodner K, Stinglmeier A, Kimberger O, Halpern K, Koelbl H, et al. Prolapse surgery versus vaginal pessary in women with symptomatic pelvic organ prolapse: which factors influence the choice of treatment? Arch Gynecol Obstet 2019;299:773-7.
4. Coolen A-LWM, Troost S, Mol BWJ, Roovers J-PWR, Bongers MY. Primary treatment of pelvic organ prolapse: pessary use versus prolapse surgery. Int Urogynecol J 2018;29:99-107.
5. Lone F, Thakar R, Sultan AH. One-year prospective comparison of vaginal pessaries and surgery for pelvic organ prolapse using the validated ICIQ-VS and ICIQ-UI (SF) questionnaires. Int Urogynecol J 2015; 26:1305-12.
6. Manchana T, Bunyavejchevin S. Validation of the Prolapse Quality of Life (P-QOL) questionnaire in Thai version. Int Urogynecol J 2010; 21:985-93.
7. Clemons JL, Aguilar VC, Tillinghast TA, Jackson ND, Myers DL. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. Am J Obstet Gynecol 2004;190:1025-9.
8. Komesu YM, Rogers RG, Rode MA, Craig EC, Gallegos KA, Montoya AR, et al. Pelvic floor symptom changes in pessary users. Am J Obstet Gynecol 2007;197:620.e1-6.
9. Coelho SCA, Marangoni-Junior M, Brito LGO, Castro EB de, Juliato CRT. Quality of life and vaginal symptoms of postmenopausal women using pessary for pelvic organ prolapse: a prospective study. Rev Assoc Med Bras (1992) 2018;64:1103-7.
10. Kuhn A, Bapst D, Stadlmayr W, Vits K, Mueller MD. Sexual and organ function in patients with symptomatic prolapse: are pessaries helpful? Fertil Steril 2009; 91:1914-8.
11. Yalcin Y, Demir Caltekin M, Eris Yalcin S. Quality of life and sexuality after bilateral sacrospinous fixation with vaginal hysterectomy for treatment of primary pelvic organ prolapse. Low Urin Tract Symptoms 2020;12:206-10.
12. Mattsson NK, Karjalainen PK, Tolppanen A-M, Heikkinen A-M, Sintonen H, Härkki P, et al. Pelvic organ prolapse surgery and quality of life-a nationwide cohort study. Am J Obstet Gynecol 2020;222:588.e1-588.e10.
13. Abdool Z, Thakar R, Sultan AH, Oliver RS. Prospective evaluation of outcome of vaginal pessaries versus surgery in women with symptomatic pelvic organ prolapse. Int Urogynecol J 2011; 22:273-8.
14. Wang Y, Han J, Zhang K, Zhu F, Yang J, Wang Y. Relevance between expectations before treatment, new symptoms and satisfaction after treatment in patients with pelvic organ prolapse. Zhonghua Fu Chan Ke Za Zhi 2015;50:664-7.
15. Thys SD, Roovers JP, Geomini PM, Bongers MY. Do patients prefer a pessary or surgery as primary treatment for pelvic organ prolapse. Gynecol Obstet Invest 2012;74:6-12.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 136-144

GYNAECOLOGY

Urinary Incontinence: Women Attending the Gynecology Outpatient Clinic Unaware of Symptoms

Montakan Srisanam, M.D.*,
Pranom Buppasiri, M.D.*,
Chompilas Chongsomchai, M.D.*,
Teerayut Temtanakitpaisan, M.D.*

** Department of Obstetrics and gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

ABSTRACT

Objectives: To determine the prevalence, symptom characteristics, risk factors and impacts on quality of life (QoL) of urinary incontinence (UI) in Thai women attending a gynecology outpatient clinic.

Materials and Methods: Voluntary female participants attending a gynecologic outpatient clinic with a complaint of gynecologic problems but not of urinary incontinence at a medical university hospital were prospectively recruited during June 2019 and January 2020. The data were collected using self-reported questionnaires. A Urogenital Distress Inventory Short Form (UDI-6) and Incontinence Impact Questionnaire-Short Form (IIQ-7) in the Thai-version were used.

Results: The total of 354 participants were enrolled. One hundred and eighty-six women (52.5%) with gynecologic symptoms had experienced urinary incontinence during the past 3 months. The prevalence of urinary incontinence increased with age, vaginal delivery, and body mass index (BMI). Stress urinary incontinence (45.2%), urgency urinary incontinence (22.0%) and mixed urinary incontinence (32.8%) were reported among unrecognized urinary incontinence participants. A high BMI and constipation were found to be the significant factors associated with developing urinary incontinence. The QoL assessment from the IIQ-7 revealed that the women in the unaware group suffered a mild impact on UI from four domains of influence including physical activity, travel, social/relationships and emotional health of QoL.

Conclusion: Urinary incontinence was commonly found in Thai women attending a gynecology outpatient clinic. Despite experiencing the symptoms, however, the majority of them rarely sought treatment. This may be due to its mild symptoms.

Keywords: prevalence, urinary incontinence, unaware urinary incontinence.

Correspondence to: *Teerayut Temtanakitpaisan, M.D., Department of Obstetrics and gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. E-mail: jacktemtanakitpaisan@hotmail.com*

Received: 30 September 2020, **Revised:** 18 December 2020, **Accepted:** 22 December 2020

การกลั้นปัสสาวะไม่อยู่: อาการที่ไม่ตระหนักในสตรีที่มาห้องตรวจผู้ป่วยนอกทางนรีเวช

มณฑกานต์ ศรีสนาม, ประนอม บุพศิริ, โฉมพิลาศ จงสมชัย, ธีระยุทธ เต็มธนะกิจไพศาล

บทคัดย่อ

วัตถุประสงค์: *เพื่อค้นหาความชุก ลักษณะอาการ ปัจจัยเสี่ยง และผลกระทบต่อคุณภาพชีวิต ของภาวะการกลั้นปัสสาวะไม่อยู่ ในสตรีไทยที่มาตรวจที่ห้องตรวจนรีเวช*

วัสดุและวิธีการ: *คัดเลือกผู้เข้าร่วมวิจัยจากสตรีที่มาเข้ารับการตรวจที่คลินิกผู้ป่วยนอกนรีเวช ด้วยปัญหาทางนรีเวชอื่นๆ ที่ไม่ใช่ภาวะกลั้นปัสสาวะไม่อยู่ ที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ในช่วงเดือนมิถุนายน 2562 ถึง มกราคม 2563 โดยรวบรวมข้อมูลจากการใช้แบบสอบถาม ที่นำแบบฟอร์มของ Urogenital Distress Inventory Short Form (UDI-6) และ Incontinence Impact Questionnaire-Short Form (IIQ-7) ฉบับภาษาไทย*

ผลการศึกษา: *มีผู้เข้าร่วมการศึกษารวมทั้งสิ้น 354 คน สตรี 186 คน (ร้อยละ 52.5) ที่มีอาการทางนรีเวช และมีอาการกลั้นปัสสาวะไม่อยู่ ในช่วง 3 เดือนที่ผ่านมา ความชุกของภาวะกลั้นปัสสาวะไม่อยู่ เพิ่มขึ้นตามอายุการคลอดทางช่องคลอด และค่าดัชนีมวลกาย ภาวะไอจามปัสสาวะเล็ด (ร้อยละ 45.2) ภาวะปัสสาวะรีบและราด (ร้อยละ 22.0) และภาวะปัสสาวะเล็ดราด (ร้อยละ 32.8) ในผู้ที่มีภาวะกลั้นปัสสาวะไม่อยู่ ค่าดัชนีมวลกายที่สูงและอาการท้องผูก พบว่าเป็นปัจจัยสำคัญที่เกี่ยวข้องกับการเกิดภาวะกลั้นปัสสาวะไม่อยู่ การประเมินคุณภาพชีวิต จาก IIQ-7 พบว่าสตรีในกลุ่มที่ละเลยอาการกลั้นปัสสาวะไม่อยู่ ได้รับผลกระทบเล็กน้อยต่อภาวะกลั้นปัสสาวะไม่อยู่ ใน 4 โดเมน (การออกกำลังกาย การเดินทาง การเข้าสังคม / ความสัมพันธ์และสุขภาพทางอารมณ์) ของคุณภาพชีวิต*

สรุป: *ภาวะกลั้นปัสสาวะไม่อยู่พบได้ทั่วไปในสตรีไทย อย่างไรก็ตามแม้มีอาการ แต่ส่วนใหญ่แทบไม่ได้เข้ารับการรักษา อาจเป็นเพราะอาการไม่รุนแรง*

คำสำคัญ: *ความชุก, ภาวะกลั้นปัสสาวะไม่อยู่, ภาวะกลั้นปัสสาวะไม่อยู่โดยไม่ตระหนัก*

Introduction

Urinary incontinence (UI) is defined as any involuntary leakage of urine by the International Continence Society (ICS)[1]. Half of adult women experience urinary incontinence[2]. The prevalence of UI varies widely among countries according to the differences in definition used and the presenting thresholds among women in different cultures[3]. The prevalence among middle aged and postmenopausal women was 44-57%[4], the prevalence was reported to be 4.8- 69.3% in Asia[5-7].

One-quarter of the affected women sought care and not more than half were given treatment. Women with UI have an increased risk of falls, fractures, sleep deficit and urinary tract infection compared to continent women[8].

Some patients may ignore the symptoms, suffer embarrassment or have a misconception about UI, which may account for the main reasons for not seeking treatments[3,9,10]. Therefore, urinary incontinence may be considerably under-reported[3]. According to the study conducted in Singapore[11], which investigated ear nose and throat (ENT) patients, almost half of the patients (41.7%) ignored the UI symptoms. This was also the case in Turkey[12], which reported the prevalence of unrecognized UI at 35.7%. The prevalence of unrecognized UI in Thai women, however, has not been investigated.

The primary outcome was aimed to determine the prevalence of UI in women who were not seeking treatments. In the current study, the term "unaware (unrecognized) of UI symptoms" was used to refer to this group of women and the secondary outcomes were aimed to describe the symptom characteristics, risk factors and impact on the quality of life (QoL) caused by UI in Thai women.

Materials and Methods

The women who attended a gynecologic outpatient clinic at a medical university hospital in the northeast of Thailand were consecutively recruited until the targeted sample size was obtained from June 2019 to January 2020. Women aged 18 years-old or over with the complaint of gynecologic problems but not UI were included, while women with urinary tract infection symptoms, cancer or pelvic organ prolapse stage 2 or more were excluded. The terms "unaware of or unrecognized" UI symptoms was used to refer to women who have UI symptoms but do not seek any treatments. All of enrolled voluntary participants completed an informed consent prior the project participation. Ethical approval was granted by the Human Research Ethics Committee, Khon Kaen University (HE621038). The data were prospectively collected of unaware UI symptoms from all participants using self-reported questionnaires. The validated Thai version of Urogenital Distress Inventory Short Form (UDI-6) was used to determine the urinary symptoms and how each symptom bothered the patient and the Incontinence Impact Questionnaire-Short Form (IIQ-7) was also used to ask about how the UI symptoms affected their activities, relationships and feelings[13]. If patients had experienced urine leakage related to the feeling of urgency, this was classified as urgency urinary incontinence (UUI). Stress urinary incontinence (SUI) was diagnosed when patients experienced urine leakage related to physical activity, coughing or sneezing. If patients had both symptoms they were assessed as mixed urinary incontinence (MUI).

The total score in each domain (physical activity, travel, social/relationships and emotional health) was converted into a range between 0 and 100. A lower score indicated better QoL; meanwhile, a higher score indicated detrimental effects on QoL.

Standardized terminology was used to describe UI that complied with the recommendations of an International Urogynecological Association (IUGA)/International Continence Society (ICS)[14]. UI symptoms were comprised of SUI that included involuntary leakage of urine on effort, physical exertion; sneezing or coughing; UUI (involuntary leakage of urine accompanied by or immediately

preceded by urgency); and MUI (involuntary leakage of urine associated with urgency and with exertion, effort, sneezing or coughing). Based on a study by Manonai et al[6], the prevalence of UI in Thai women in the rural area was 36.5%. This assumed the prevalence of UI in the hospital may be at least or higher than in the community setting. To achieve a power of 80% and a level of significance of 5%, at least 354 patients were required.

Statistical analyses

Statistical analysis was performed using SPSS program version 13.0. Normality testing was conducted using Kolmogorov-Smirnov testing. The descriptive data were expressed as percentages, means, and medians. The chi squared test was employed to evaluate factors associated with UI. A p value of < 0.05 were considered statistically significant. Multiple logistic regression analysis (forward stepwise) was used for multivariate analysis.

Results

Three hundred and ninety patients were contacted, fifteen patients refused to participate in the study. A total of 375 voluntary participants were offered the questionnaires. Only 354 voluntary participants, however, completed the questionnaires; the response rate was 94.4%. One hundred and eighty-six women (52.5%) who attended the gynecologic clinic with the complaint of gynecologic symptoms, except UI, had experienced UI symptoms during the past 3 months.

Among participants unaware of UI symptoms, 45.2% (84 women) had SUI; 22.0% (41 women) had UUI; and 32.8% (61 women) had MUI.

The baseline characteristics of participants are shown in Table 1. Age, body mass index (BMI), the history of vaginal birth and constipation were significantly different from normal.

Table 1. Characteristics of participants (n = 354).

Variables	With UI (n=186)	Without UI (n=168)	p value
Age (years), mean (SD)	44.30 (10.07)	40.51(10.64)	0.0007
BMI (kg/m^2), mean (SD)	24.21 (3.99)	22.89 (3.82)	0.0017
Comorbidity, n (%)			
Yes	121 (65.05)	121 (72.02)	0.159
No	65 (34.95)	47 (27.98)	
Education level, n (%)			
- No formal schooling	1 (0.53)	0 (0.00)	0.492
- Primary school	24 (12.90)	14 (8.33)	
- Secondary school	35 (18.81)	29 (17.30)	
- Vocational/Technical/College	18 (9.70)	16 (9.50)	
- University	108 (58.06)	109 (64.88)	
Vaginal delivery, n (%)			
- Yes	111 (59.70)	70 (41.67)	0.001
- No	75 (40.30)	98 (58.33)	
Sexually active, n (%)			
- Yes	137 (73.66)	123 (73.21)	0.925
- No	49 (26.34)	45 (26.79)	

Table 1. Characteristics of participants (n = 354). (Cont.)

Variables	With UI (n=186)	Without UI (n=168)	p value
Occupation, n (%)			
- Unemployed	5 (2.69)	7 (4.20)	0.077
- Labor	4 (2.15)	1 (0.60)	
- Employment	12 (6.45)	5 (2.98)	
- Agriculture	27 (14.52)	11 (6.55)	
- Government service	57 (30.65)	56 (33.33)	
- Trade	17 (9.14)	16 (9.50)	
- Other	64 (34.40)	72 (42.86)	
Constipation, n (%)			
- Yes	18 (9.70)	6 (3.57)	0.022
- No	168 (90.30)	162 (96.43)	
Menopausal status, n (%)			
- Yes	46 (24.73)	38 (22.62)	0.641
- No	140 (75.27)	130 (77.38)	

UI: urinary incontinence, BMI: body mass index, SD: standard deviation

The prevalence of UI increased with age, vaginal delivery, and BMI as shown in Table 2.

Age, BMI, vaginal delivery and constipation were identified as the potential risk factors for developing UI (Table 3). Women aged 40-59 years were more than twice as likely to have UI than those aged 18-39 years (odds ratio (OR) 2.28, 95% confidence interval (CI) 1.44-3.58). The obese participants (BMI > 30 kg/m^2) were more than three times as likely to have UI than normal weight participants (OR 3.16, 95%CI 1.29-7.75). Moreover, vaginal delivery and constipation (fewer than 3 times a week) were more than twice as likely to have UI (OR 2.07, 95%CI 1.35-3.16 and OR 2.89, 95%CI 1.12-7.47).

Table 2. Prevalence of unaware urinary incontinence symptoms in various subgroups.

Variables	Number of UI women	Prevalence of UI	95% CI
Age (years)			
18-39	48	39.02	30.35 - 48.23
40-59	127	59.35	52.43 - 65.98
≥ 60	11	64.71	38.32 - 85.79
Vaginal delivery			
- Yes	111	61.33	53.81 - 68.45
- No	75	43.35	35.85 - 51.08
Sexually active			
- Yes	137	52.69	46.43 - 58.89
- No	49	53.13	41.57 - 62.54
BMI (kg/m^2)			
< 18.5	9	39.13	19.70 - 61.45
18.5 - 24.9	107	48.64	41.86 - 55.44
25 - 29.9	49	59.04	47.69 - 69.71
≥ 30	21	75	55.12 - 89.30

UI: urinary incontinence, CI: confidence interval

Table 3. Unadjusted odds ratios (OR) of potential risk factors for unaware urinary incontinence symptoms.

Variables	Number of women	Unadjusted OR	95% CI	p value
Age (years)	354	1.03	1.01 - 1.05	0.001
18 - 39	123	Reference		
40 - 59	214	2.28	1.44 - 3.58	< 0.001
≥ 60	17	2.86	0.99 - 8.25	0.051
BMI (kg/m^2)				
< 18.5	23	0.67	0.28 - 1.63	0.387
18.5 - 24.9	220	Reference		
25 - 29.9	83	1.52	0.91 - 2.53	0.107
≥ 30	28	3.16	1.29 - 7.75	0.012
Comorbidity				
- Yes	242	1.38	0.80 - 2.17	0.160
- No	112	Reference		
Education level				
- No formal schooling + Primary school	39	1.80	0.88 - 3.65	0.102
- Secondary school	64	1.21	0.69 - 2.13	0.490
- Vocational/Technical/College	34	1.13	0.55 - 2.34	0.731
- University	217	Reference		
Vaginal delivery				
- Yes	181	2.07	1.35 - 3.16	0.001
- No	173	Reference		
Sexually active				
- Yes	260	1.02	0.63 - 1.64	0.925
- No	94	Reference		
Occupation				
- Unemployed	12	Reference		
- Labor	5	5.60	0.47 - 66.44	0.172
- Employment	17	3.36	0.71 - 15.84	0.126
- Agriculture	38	3.43	0.89 - 13.18	0.072
- Government service	113	1.42	0.42 - 4.75	0.565
- Trade	33	1.48	0.39 - 5.65	0.560
- Other	136	1.24	0.37 - 4.11	0.720
Constipation				
- Yes	24	2.89	1.12 - 7.47	0.028
- No	330	Reference		
Menopausal status				
- Yes	84	1.12	0.68 - 1.83	0.641
- No	270	Reference		

CI: confidence interval

When multivariate analysis was used, using the forward stepwise method that adjusted the possible risk factors for UI and by entering all significant factors ($p < 0.2$) (including age, BMI, vaginal delivery and constipation), the analysis revealed that only BMI and constipation remained as statistically significant risk factors associated with an increased likelihood of having UI (Table 4).

Table 4. Adjusted odds ratios (OR) of potential risk factors for unaware urinary incontinence symptoms.

Variables	Adjusted OR	95% CI	p value
Age (years)	1.02	1.00 - 1.05	0.028
BMI	1.08	1.02 - 1.15	0.004
Vaginal delivery	1.50	0.93 - 2.44	0.098
Constipation	3.36	1.26 - 8.92	0.015

Adjusted age, BMI, vaginal delivery and constipation
CI: confidence interval, BMI: body mass index

To investigate QoL using IIQ-7 and severity of each of the UI symptoms, four domains were evaluated, including physical activity, travel, social/relationships and emotional health. The median scores of four domains in unaware SUI symptoms were 0, 16.66, 0 and 0; in unaware UUI scores 0, 16.66, 16.66 and 0; and 0, 16.66, 16.66 and 0 in unaware MUI (Table 5). This might indicate that the women in the unaware groups only suffered a mild impact on UI on QoL.

As for healthcare-seeking behavior in the subjects unaware of UI symptoms, 65.1% (121 patients) thought that the UI symptoms did not bother them and 32.3% (60 patients) thought that it was a normal part of the aging process.

Table 5. Quality of life scores regarding each type of urinary incontinence (IIQ-7).

	Physical activity (0-100)	Travel (0-100)	Social/ Relationships (0-100)	Emotional health (0-100)
Stress urinary incontinence (score), median (IQR)	0 (0, 16.66)	16.66 (0, 33.33)	0 (0, 33.33)	0 (0, 16.66)
Urgency urinary incontinence (score), median (IQR)	0 (0, 16.66)	16.66 (0, 33.33)	16.66 (0, 33.33)	0 (0, 16.66)
Mixed urinary incontinence (score), median (IQR)	0 (0, 16.66)	16.66 (0, 33.33)	16.66 (0, 33.33)	0 (0, 16.66)

IQR: interquartile range

Discussion

The prevalence of UI in women seeking healthcare for non-UI related symptoms in a gynecology clinic was 52.5%. Among participants unaware of UI, the prevalence was considerably high similar to the study by Luo et al who investigated the prevalence in Singapore[11]. It was reported 41.7% in ENT patients. These findings were consistent with a study which reported the prevalence of hidden UI 35.7% in Turkey[12]. The high rate of hidden UI may suggest that if the prevalence was collected solely from the complaint symptoms, the actual prevalence may be under reported.

Advancing age is established as the potential risk of UI[15]. Based on the multivariate logistic regression, in the case of hidden symptoms, BMI and constipation were significant factors associated with developing UI. The findings of this current study did not support the data from Luo et al[11] who studied ENT patients, revealed that age, vaginal delivery and being sexually active were associated with urinary incontinence. The differences in those risk factors may be due to the different settings of patients in the gynecologic clinic and ENT clinic. Moreover, the studies in Thailand on the risk of UI revealed that chronic cough, chronic constipation, vaginal delivery, menopause were reported in women younger than 50 years of age. Furthermore, never receiving hormone therapy and high

BMI were the risk factors associated with UI in postmenopausal women[16-18].

Despite the high prevalence of hidden UI among Thai women, most patients overlooked the urinary symptoms. According to the scores of Thai version IIQ-7, the median scores of SUI, UUI and MUI were significantly low. It may be the case that the unaware patients had only mild symptoms which might not affect their daily life such as physical activity, travel, social/ relationships and emotional health. The results matched the data of those observed in Singapore and Turkey[5,13]. Consistent with the findings of Cetinel et al[12] and Cooper et al[19], the patients were not likely to seek treatment. This may be because the symptoms were not disturbing their daily life activities (see the QoL scores). Whereas the QoL scores in symptomatic UI women were more significantly impaired than control in postmenopausal women[20].

Some unaware patients perceived that UI was the normal process of aging. The data from Singapore also claimed the same reasons for not seeking health care[14]. Therefore, it was argued from the study that the knowledge of UI symptoms, factors and treatment options should be transferred to general public in order to raise public awareness. Moreover, in the case of mild symptoms, behavioral and lifestyle modifications such as weight reduction, fluid management, bladder training and pelvic floor muscle training were considered the first line therapy with a 50% reduction of incontinence episodes[21]. Despite the high prevalence of hidden UI, one third believed that the condition was a stage of aging process. Thus, to alleviate and improve QoL of patients with unrecognized UI, UI symptoms should be addressed in gynecologic clinics during history taking even though patients come with gynecologic problems not with UI problems. To prevent the worsening of the UI symptoms, behavioral and lifestyle modification should be counseled to patients with UI symptoms.

The present study was based on a prospective study illustrating the prevalence of the unawareness of UI among Thai women who came with the gynecologic symptom complaints but not of UI at a hospital setting. This may not represent the cases in the community. The lack of generalization, lack of physical examination and objective data regarding UI such as a pad test were considered as limitations to this study.

Conclusion

Urinary incontinence appeared to be a common disease among Thai women. It was the case, however, that even though experiencing the UI symptoms, the majority of the patients nevertheless, rarely sought treatment due to the mild symptoms and they were inclined to consider the problem as one of the aging process.

Acknowledgements

We would like to thank Professor James Arthur Will for editing the manuscript via the Publication Clinic KKU, Thailand.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
2. Minassian VA, Stewart WF, Wood GC. Urinary incontinence in women: variation in prevalence estimates and risk factors. Obstet Gynecol 2008;111:324-31.
3. Elbiss HM, Osman N, Hammad FT. Social impact and healthcare-seeking behavior among women with urinary incontinence in the United Arab Emirates. Int J Gynaecol Obstet 2013;122:136-9.
4. Kinchen KS, Lee J, Fireman B, Hunkeler E, Nehemiah JL, Curtice TG. The prevalence, burden, and treatment of urinary incontinence among women in a managed care plan. J Womens Health 2007;16:415-22.
5. Ju CC, Swan LK, Merriman A, Choon TE, Viegas O. Urinary incontinence among the elderly people of Singapore. Age Ageing 1991;20:262-6.
6. Manonai J, Poowapirom A, Kittipiboon S, Patrachai S, Udomsubpayakul U, Chittacharoen A. Female urinary incontinence: a cross-sectional study from a Thai rural area. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:321-5.
7. Tsai Y-C, Liu C-H. Urinary incontinence among Taiwanese women: an outpatient study of prevalence,

comorbidity, risk factors, and quality of life. Int Urol Nephrol 2009;41:795-803.
8. Lukacz ES, Santiago-Lastra Y, Albo ME, Brubaker L. Urinary incontinence in women: a review. JAMA 2017;318:1592-604.
9. Hsieh C-H, Su T-H, Chang S-T, Lin S-H, Lee M-C, Lee MY. Prevalence of and attitude toward urinary incontinence in postmenopausal women. Int J Gynaecol Obstet 2008;100:171-4.
10. Perera J, Kirthinanda DS, Wijeratne S, Wickramarachchi TK. Descriptive cross sectional study on prevalence, perceptions, predisposing factors and health seeking behaviour of women with stress urinary incontinence. BMC Womens Health 2014;14:78.
11. Luo R, Dai W, Tay LH, Ng FC, Koh L-T. Urinary incontinence in female outpatients in Singapore. Int Urogynecol J2018;29:579-84.
12. Cetinel B, Demirkesen O, Tarcan T, Yalcin O, Kocak T, Senocak M, et al. Hidden female urinary incontinence in urology and obstetrics and gynecology outpatient clinics in Turkey: what are the determinants of bothersome urinary incontinence and help-seeking behavior? Int Urogynecol J Pelvic Floor Dysfunct 2007;18:659-64.
13. Weerasopone S, Santingamkul A. Validation of the Thai version of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6). Chulalongkorn Med J 2016;60:389-98.
14. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecology J 2010;21:5-26.
15. Xu C, Chen M, Fu J, Meng Y, Qin S, Luo Y. Urinary incontinence status and risk factors in women aged 50-70 years: a cross-sectional study in Hunan, China. Int Urogynecol J 2021;32:95-102
16. Bunyavejchevin S. Risk factors of female urinary incontinence and overactive bladder in Thai postmenopausal women. J Med Assoc Thai 2005;88 (Suppl 4):S119-123.
17. Jueng-Anuwat P, Roongruangsilp U, Kochakarn W, Ratana-Olarn K. Risk factors for stress urinary incontinence in middle aged and elderly Thai women. J Med Assoc Thai 2001;84:1121-5.
18. Sakondhavat C, Choosuwan C, Kaewrudee S, Soontrapa S, Louanka K. Prevalence and risk factors of urinary incontinence in Khon Kaen menopausal women. J Med Assoc Thai 2007;90:2553-8.
19. Cooper J, Annappa M, Quigley A, Dracocardos D, Bondili A, Mallen C. Prevalence of female urinary incontinence and its impact on quality of life in a cluster population in the United Kingdom (UK): a community survey. Prim Health Care Res Dev 2015;16:377–82.
20. Bunyavejchevin S. The impact of overactive bladder, stress and mixed urinary incontinence on quality of life in Thai postmenopausal women. J Med Assoc Thai 2006;89:294-8.
21. Committee on Practice Bulletins. ACOG Practice Bulletin No. 155: Urinary incontinence in women. Obstet Gynecol 2015;126:e66-81.

Thai Journal of Obstetrics and Gynaecology
March 2022, Vol. 30, No. 2, pp. 145-149

CASE REPORT

Diagnosis of Pentalogy of Cantrell with Craniorachischisis at 11 weeks on 2 Dimensional Ultrasound - A rare case report

Pranadeep Reddy Inukollu, MBBS, MS*,
Sai Bhavana D, M.D.**,
Shivangini Gupta, M.D.***,
Divya Solipuram, MS****,
Shyamala G, MS.*

** Department of Obstetrics and Gynecology, Kasturba Medical College, Manipal, Manipal University (MAHE), India*
*** ESIC MCH, Hyderabad, Telangana, India*
**** GMERS Medical College and Hospital, Vadodara, Gujarat, India*
***** Vijaya Chander Clinic, Hyderabad, India*

ABSTRACT

Pentalogy of Cantrell (PC) is an extremely rare congenital malformation, with estimated incidence from 5.5 to 7.9 per million live births. Diagnosed in second trimester or beyond with first trimester detection in hand full of cases and 2 case reports at 11 weeks in literature. An unusual combination of PC with craniorachischisis, has been reported by a few at 18-26 weeks with one at 12 weeks. Ours is the first ever presented case report diagnosed as early as 11 weeks. This patient was diagnosed with PC and craniorachischisis at 11 weeks by 2D ultrasound who underwent pregnancy termination. Presence of a throracoabdominal defect at such early gestation should alert sonologists to include PC in differentials. This rare combination of dorsal and ventral midline defects occurring at a similar embryologic timeline could point to a common inciting event that needs to be further investigated.

Keywords: pentalogy of cantrell, cantrell syndrome, craniorachischisis, first trimester ultrasound.

Correspondence to: *Pranadeep Reddy Inukollu, MS, Department of Obstetrics and Gynecology, Kasturba Medical College, Manipal Manipal University (MAHE), Manipal 576104, India. E-mail: pranadeep_inukollu@yahoo.com*

Received: 17 February 2021, **Revised:** 5 July 2021, **Accepted:** 4 August 2021

Introduction

First described by Cantrell in 1958, pentalogy of Cantrell (PC) is a constellation of five defects that includes lower sternum defect, a midline supraumblical thoracoabdominal wall defect, a defect of anterior diaphragm, a defect of diaphragmatic pericardium and congenital cardiac anomalies[1].

Although case reports of such patterns date back to early 1700s, it was Cantrell in 1958 who unified this pattern into a clinical syndrome, proposed its pathophysiology and clinical management, majority of which holds true even 6 decades later barring certain advances in postnatal approaches that improved survival in certain subtypes.

Case:

A 28 years old third gravida with nil significant previous obstetric history, presented to us for routine antenatal care. Pregnancy was from a non consanguineous marriage without a history of congenital defects or chromosomal anomalies or medical disorders. She was on folic acid supplementation. Aneuploidy scan at 11 1/7 weeks done using Voluson P8 showed a crown rump length (CRL) of 30 mm corresponding to 10 weeks and nuchal translucency (NT) could not be measured, abdominal contents freely floating in the amniotic fluid outside the abdominal cavity. Heart was located outside the thoracic cavity with good cardiac activity as shown in Fig. 1. Diaphragm appeared to be slightly elevated. Better and precise delineation of intracardiac, diaphragmatic and sternal defects would require scan at a later gestation. Cranial vault was not formed and a vertebral bony defect was noted posteriorly with exposed neural tissue extending up to the lumbar area. A comparison of the neural tube defect in the antenatal scan and the expelled fetus are shown in Fig. 2. The findings were a peculiar combination of dorsal and ventral midline defects including ectopia cordis, omphalocoele/gastroschisis, eventuation and craniorachischisis. A presumptive diagnosis of PC with craniorachischisis was made.

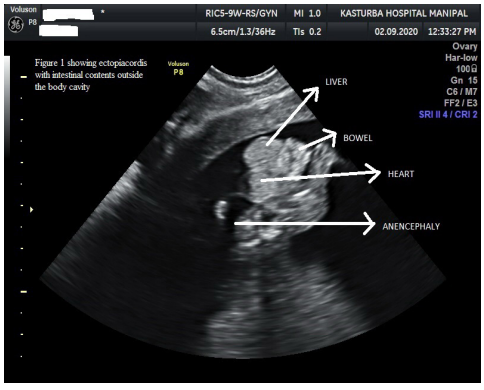


Fig. 1. Image showing abdominal contents and heart outside the body cavity.

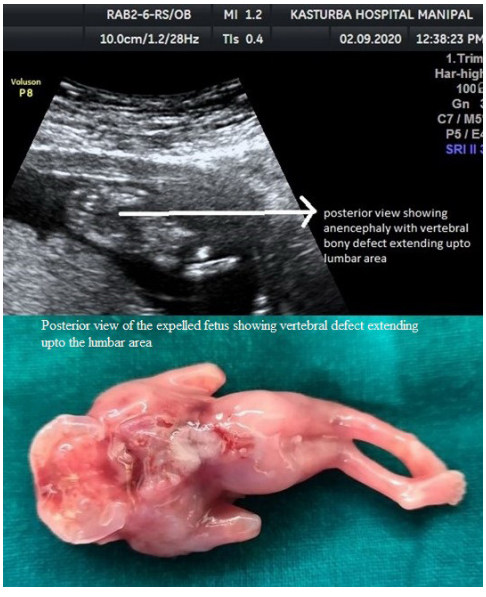


Fig. 2. Comparison of the vertebral defect in the antenatal scan and after expulsion of the fetus.

Though diagnosis of anterior abdominal wall defect cannot be made before 12 weeks of gestation, we suspected a probable gastroschisis since it was also associated with ectopia cordis and dorsal midline defects. PC has a varied presentation and the prognosis depends greatly on the severity of condition, especially the ectopia cordis, intracardiac defects, extent of thoracoabdominal defect and its associated anomalies. The associated craniorachischisis in this

patient is a lethal condition which was explained to the couple in detail who opted for pregnancy termination. The couple deferred genetic evaluation, karyotype analysis and autopsy. Termination of pregnancy was done at 12 weeks using 400 micrograms of vaginal misoprostol tablets every 3 hour for 3 doses (which is half the usual dose as per the International Federation of Gynecology and Obstetrics protocol as this patient is a case of previous low transverse cesarean section). A dead male fetus of 130 g was expelled after 3rd dose. Gross examination of the fetus showed anencephaly with prominent orbits and absence of posterior vertebral elements with splaying of the lamina and exposed spinal cord involving up to lumbar vertebrae, suggestive of craniorachischisis totalis. There was a lower sternal defect with the heart noted outside chest wall and upper abdominal wall defect with exposed stomach and intestines without a covering membrane suggestive of gastroschisis. These findings are shown in Fig. 3, 4. Upper and lower limbs, anus and external genitalia appeared normal.

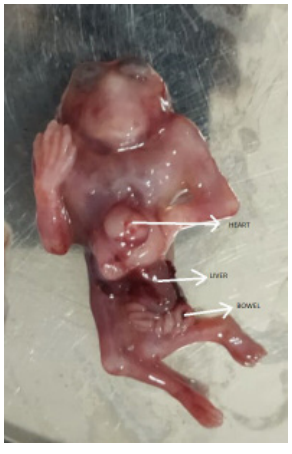


Fig. 3. Anterior view showing anencephaly with protruding orbits with heart, liver and bowel outside the body cavity.

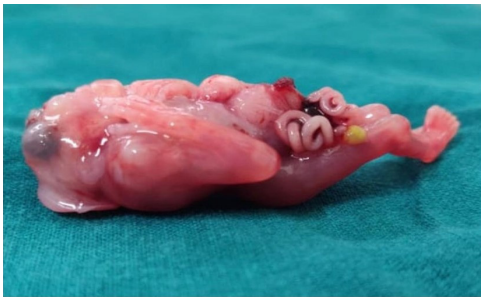


Fig. 4. Lateral view showing anenchephaly and thoracoabdominal defect.

Discussion

Around 250 cases of PC have been reported to date with entire spectrum occurring rarely[2]. The pathogenesis originally described by Cantrell (1958) occurs between 14 and 18 days of embryonic life. First the defects in anterior diaphragm, inferior pericardium and heart occur due to anomalous development of septum transversum and its adjacent somatic and splanchnic mesoderm. Second, abdominal wall defects occur due to defective attachment of abdominal

musculature to the improperly formed primordial sternum[1]. Craniorachischisis is the open cranial defect (anencephaly/exencephaly) continuous with a complete spinal dysraphism and represents a complete failure of neurulation resulting from dysmorphogenesis occurring no later than 20-22 days after conception, which coincides with occurrence of PC on the embryologic timeline[3]. It is proposed that time point of embryogenetic insult decides extent and severity of malformation. Hence this explains wide spectrum of PC and associated neural tube defects (NTD) reported so far, including ours which describes one of the severe types of NTDs where the inciting event must have probably occurred very early in the timeline of embryogenesis. Co-occurrence of such ventral and dorsal midline defects suggests possibility of common genetic and environmental factors behind their coexistence that has to be addressed in future research.

Any genetic factors and etiological causes related to PC are unknown. Though a possibility of familial inheritance and association with chromosomal anomalies like trisomy 18, 13 and Turners syndrome has been suggested, cases have been sporadic in occurrence mostly[4].

Toyama in 1972 proposed a classification that grouped various cases with less than 5 defects and incomplete presentations as subtypes of Cantrell syndrome[5]. Recent studies have stressed that strict classification is not as important as a thorough description and understanding of congenital abnormalities in utero. Similarly, Coleman et al studied PC and two closely related syndromes with overlapping features namely OEIS (omphalocoele, exstrophy, imperforate anus, spina bifida) and limb-body wall complex (LBWC) as a spectrum of diseases resulting from improper closure of lateral and craniocaudal folds. They concluded that degree of pulmonary hypoplasia was far more indicative of prognosis than any specific classification system per se. In counseling families, planning delivery and management, a descriptive diagnosis is more valuable than trying to line characteristics up with a specific syndrome or a subtype within syndrome[6].

Diagnosis of PC in first trimester was first described by Bennett, using 2D sonography at 12 weeks[7]. Subsequently few more cases at 12-13 weeks have been published[8]. Earliest diagnosis at 11 weeks was done in two case reports apart from ours which described an associated single umbilical artery and called it "hexology"[9] and the other had associated limb defect and lardoscoliosis[10] which were not seen in our case. However our patient had an associated craniorachischisis additionally. A large retrospective analysis over a period of 9 years done on 100,997 pregnancies to evaluate performance of first trimester scan on detection of non-chromosomal anomalies showed fetal anomalies in 1.7% pregnancies with 27.6% of the anomalies being detected during 11 to 13 weeks gestation while 53.8% detected on the second trimester scan and 18.6% detected in the third trimester or postnatally. There were only 2 reported cases of PC in this study both of which were detected in first trimester scan. However, there was no associated craniorachischisis in these cases[11].

Another retrospective analysis was done on 6,366 twin pregnancies between 2002 and 2019 to analyze the performance of 11 to 13 weeks scan in detection of fetal anomalies which had one case of isolated PC without craniorachischisis that was detected in first trimester. The prevalence of this anomaly in twin gestation was said to be 1 in 12,732 compared to 1 in 50,499 among singleton pregnancies[12].

A systematic review on 67 total reported cases of PC diagnosed in the first trimester of pregnancy (published from January 1980 to July 2019) suggested that ultrasound findings of a coexistent omphalocele and ectopia cordis at 11 to 13 weeks scan is highly suggestive of PC[13].

PC in association with craniorachischisis was reported at 12 weeks using 3D ultrasound[14]. Present case report is first of its kind in reporting PC in combination with craniorachischisis by 2D ultrasound at 11 weeks. Early diagnosis in first trimester will assist in early pregnancy termination thereby limiting the physical and emotional anguish to the couple.

We conclude that though the intricate details of

the syndrome may not be appreciable at such early gestation, presence of a thoraco-abdominal defect should alert the sonologists to include PC in differentials and look for associated anomalies that can improve patient care.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Cantrell JR, Heller RJA, Ravitch MM. A syndrome of congenital defects involving the abdominal wall, sternum, diaphragm, pericardium, and heart. Surg Gynecol Obstet 1958;107:602-14.
2. Jnah AJ, Newberry DM, England A. Pentalogy of Cantrell: case report with review of the literature. Adv Neonatal Care 2015;15:261-8.
3. Wahab S, Sahoo B, Mittal S, Khan RA. Prenatal diagnosis of pentalogy of cantrell in a case with craniorachischisis. Curr Pediatr Res 2017;21:8-10.
4. Smigiel R, Jakubiak A, Lombardi MP, Jaworski W, Slezak R, Patkowski D, Hennekam RC. Co-occurrence of severe Goltz-Gorlin syndrome and pentalogy of Cantrell - Case report and review of the literature. Am J Med Genet A 2011;155:1102-05.
5. Toyama WM. Combined Congenital defects of the anterior abdominal wall, sternum, diaphragm, pericardium and heart: a case report and review of the syndrome. Pediatrics 1972;50:778-9.
6. Coleman PW, Marine MB, Weida JN, Gray BW, Billmire DF, Brown BP. Fetal MRI in the identification of a fetal ventral wall defect spectrum. Am J Perinatol Rep 2018;8:e264-e276.
7. Bennett TL, Burlbaw J, Drake CK, Finley BE. Diagnosis of ectopia cordis at 12 weeks gestation using transabdominal ultrasonography with color flow Doppler. J Ultrasound Med 1991;10:695-6.
8. Türkçapar AF, Sargın Oruc A, Öksüzoglu A, Danışman N. Diagnosis of pentalogy of cantrell in the first trimester using transvaginal sonography and color Doppler. Case Rep Obstet Gynecol 2015:2015:179298.
9. Kubba T, Khalil A, Abu-Rustum R, Aoun A, Scott R, Abi-Nader K, Pandya P. Prenatal diagnosis of pentalogy of Cantrell at 11-13 weeks: Evidence for a hexalogy. J Obstet Gynaecol 2013;33:85-6.
10. Ergenoğlu MA, Yeniel AÖ, Peker N, Kazandı M, Akercan F, Sağol S. Prenatal diagnosis of Cantrell pentalogy in first trimester screening: case report and review of literature. J Turk Ger Gynecol Assoc 2012;13:145-8.
11. Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2019;54:468-76.
12. Syngelaki A, Cimpoca B, Litwinska E, Akolekar R, Nicolaides KH. Diagnosis of fetal defects in twin pregnancies at routine 11-13-week ultrasound examination. Ultrasound Obstet Gynecol 2020;55:474-81.
13. Grigore M, Micu R, Matasariu R, Duma O, Chicea AL, Chicea R. Cantrell syndrome in the first trimester of pregnancy: imagistic findings and literature review. Med Ultrason 2020;22:189-96.
14. Murata S, Nakata M, Sumie M, Mastsuabra M, Sugino N. Prenatal Diagnosis of Pentalogy of Cantrell With Craniorachischisis by Three-Dimensionalultrasonography in the First Trimester. Taiwan J Obstet Gynecol 2009;48:317-8.