ISSN 0857-6084

# THAI JOURNAL OF OBSTETRICS AND GYNAECOLOGY

THE OFFICIAL JOURNAL OF
THE ROYAL THAI COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

VOL. 32 NO. 4 July - August 2024

# 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.
C. Matatratip, M.D.

# 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**


## Editor in Chief


**PHUPONG Vorapong**

King Chulalongkorn Memorial Hospital, Chulalongkorn University, Thailand


## International Editorial Board:




**Manager:** Prof. Vitaya Titapant, M.D.
**Assistant Manager:** Arissara Puangmalee, B.A.
**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



**Website:** www.tci-thaijo.org, E-mail: vorapong.p@chula.ac.th

## 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 article (invited), Original article, Case report
**Frequency:** 6 issues per year (January-February, March-April, May-June, July-August, September-October, November-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)

**Direction to contributors.** All papers should be sent to Editor, Thai Journal of Obstetrics and Gynaecology, 8th Floor, The Royal Golden Jubilee Bldg. 2, Soi Soonvijai, New Petchburi Road, Bangkapi, Bangkok 10310, Thailand. 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 (http://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 Thai Journal of Obstetrics and Gynaecology 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 Thai Journal of Obstetrics and Gynaecology. 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 Conclusions, each with a brief adequate presentation. Abstracts for case reports should not exceed 50 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.

**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.

**Ethical consideration.** Each author's contribution to the paper is to be quantified. Authors must state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken.

**Publication Ethics and Publication Malpractice Statement.** The publication ethics is required for publication in *Thai J Obstet Gynaecol*. The publication ethics guidelines are followed the *Committee on Publication Ethics-COPE (http://publicationethics.org/)*.

***Editor of Thai Journal of Obstetrics and Gynaecology***

1. strive to meet the needs of readers and authors, constantly improve the journal.

2. have processes in place to assure the quality of the material published.

3. give timely and comprehensive feedback to authors.

4. maintain the integrity of the academic record and preclude business needs from compromising intellectual and ethical standards.

5. are willing to publish corrections, clarifications, retractions and apologies when needed.

6. seek the views of authors, readers, reviewers and editorial board members about ways of improving the journal's processes.

7. encourage and being aware of research into peer review and publishing and reassessing the journal's processes in the light of new findings.

8. endeavor to ensure that research published was carried out according to the relevant internationally accepted guidelines (e.g. the Declaration of Helsinki for clinical research, the AERA and BERA guidelines for educational research).

9. seek assurances that all research has been approved by an appropriate body (e.g. research ethics committee, institutional review board).

10. have a duty to act if editors suspect misconduct or if an allegation of misconduct is brought to editors.

11. pursue misconduct for the following reasons in published and unpublished work: plagiarism of other works, data fabrication and falsification, when a submitted manuscript has been found to be under revision elsewhere or published elsewhere, or where there is citation manipulation.

12. make decisions to accept or reject a paper for publication based on the paper's importance, originality and clarity, and the study's validity and its relevance to the remit of the journal.

13. respect requests from authors that an individual should not review their submission, if these are well reasoned and practicable.

***Authors who submit articles to TJOG should***

1. Report the research conducted in an ethical and responsible manner and comply with all relevant legislation.

2. Present the results clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

3. Strive to describe the methods clearly and unambiguously so that the findings can be confirmed by others.

4. Adhere to publication requirements that submitted work is original, is not plagiarized, and has not been published elsewhere.

5. Take collective responsibility for submitted and published work.

6. Confirm that the authorship of research publications should accurately reflect individuals' contributions to the work and its reporting.

7. Disclose funding sources and relevant conflicts of interest.

***Reviewers of TJOG should***

1. Only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner

2. Respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal

3. Declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest

4. Not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations

5. Be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments

6. Acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner

7. Provide journals with personal and professional information that is accurate and a true representation of their expertise

8. Recognize that impersonation of another individual during the review process is considered serious misconduct.

**Article processing charge.** To publish in Thai J Obstet Gynaecol, authors are required to pay an article processing charge (APC). The APC for all published papers is $150. Members of RTCOG have 50% discount for APC.

**Subscription.** Thai Journal of Obstetrics and Gynaecology is published every three months. The annual subscription rate is US$ 50 post free by surface mail. Order for subscription, business correspondences and advertising space should be addressed to the editor.

# 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. 32 No. 4 July - August 2024**


# CONTENTS

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 255-256.

## EDITORIAL

# Intriguing Review and Topics in Fourth Issue of Thai Journal of Obstetrics and Gynaecology 2024

Vorapong Phupong, M.D., FRTCOG.*

** Editor in Chief, Thai J Obstet Gynaecol, The Royal Thai College of Obstetricians and Gynaecologists*

This fourth issue of Thai Journal of Obstetrics and Gynaecology 2024 contains many interesting articles. The special article is "update on amniocentesis". This article aims for updating of amniocentesis in pregnant women with specific conditions, such as those infected with human immunodeficiency virus, those taking aspirin, those who are obese, those who are infected with hepatitis B virus, and those experiencing a twin pregnancy[1].

This issue also contains six original articles and two case reports. Sirisakpanich et al performed a retrospective chart review to compare the differences of pelvic organ prolapse quantification (POP-Q) measurements obtained preoperatively at the outpatient setting and intraoperatively with instrumental traction during full anesthetization in patients undergoing vaginal reconstructive surgery and found that POP-Q measurements obtained during conventional outpatient examination provided less prolapse severity[2]. Pinnington et al performed a retrospective study to determine the performance of the combined first trimester Down syndrome screening test and the appropriate cut-off points for intermediate-risk identification. They found that the combined first-trimester screening test had a detection rate of 75%, and a high specificity and accuracy of 94%. The recommended cut-off point for intermediate risk was between 1:251 and 1:1,000[3]. Sareerat et al performed a randomized, controlled study to compare the two different antenatal nutritional counseling styles [computer-assisted instruction (CAI) and routine, casual, individual (RCI)] regarding the proper gestational weight gain (GWG) of healthy pregnant women during the second trimester, and to identify the factors influencing the level of pregnant women's GWG. They found that antenatal nutritional counseling using CAI was shown to be comparable to RCI in trying to achieve an appropriate GWG. The multiparous individuals had significant factors for having an appropriate GWG[4]. Polyota et al performed a randomized controlled trial to evaluate the effect of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs on the controlling of abnormal uterine bleeding in hormonal subdermal implant users and found that conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding in etonogestrel subdermal implant use[5]. Achavangkool et al performed a cross-sectional, questionnaire-based study to determine the prevalence of depressive symptoms among Thai reproductive-aged woman with polycystic ovary syndrome (PCOS) and to identify factors associated with depression. The study revealed the prevalence of depression was 39.9%. A lack of savings from income was a significant factor associated with depression[6]. Sangnucktham et al performed a study to find the validity and reliability of Thai version of the overactive bladder questionnaire short form (OAB-q SF) and the correlation of Thai version OAB-q SF to Thai version overactive bladder questionnaire (OAB-q). They found that Thai version of the OAB-q SF showed good psychometric properties (reliability and validity) for

measuring the OAB symptom severity and health related quality of life. There was very strong correlation between Thai version of OAB-q SF and OAB-q[7].

Regarding two case reports, Horibe et al reported a rare case of mesonephric-like adenocarcinoma arising from the ovary and reviewed the literature[8]. Jayasakoon et al also reported a uncommon case of twin pregnancy presenting with hydatidiform mole and co-existing living fetus with ovarian venous thrombosis[9].

The RTCOG 39th annual meeting will be held during 29 October - 1 November 2024 at Dusit Thani, Pattaya, Chonburi, Thailand. The theme of the meeting is "Optimizing OBGYN". Wish to see you at RTCOG Annual Meeting 2024 at Dusit Thani, Pattaya, Chonburi, Thailand.

## References


1. Hanprasertpong J, Hanprasertpong T. Update on amniocentesis. Thai J Obstet Gynaecol 2024;32:257-60.
2. Sirisakpanich K, Wechchasart K. A comparison of conventional outpatient and instrumental intraoperative pelvic organ prolapse quantification measurements in patients undergoing vaginal surgery for pelvic organ prolapse. Thai J Obstet Gynaecol 2024;32:261-8.
3. Rekhawasin TP, Arthan J, Komoltri C, Chanprapaph P. Accuracy of the combined first trimester down syndrome screening test and the optimum range of the cut-off point for intermediate-risk identification: Twelve years' experience. Thai J Obstet Gynaecol 2024;32:269-77.
4. Sareerat S, Kongsomboon K, Hanprasertpong T. Comparing the different antenatal nutritional counseling methods regarding proper gestational weight gain during the second trimester: A randomized, controlled trial. Thai J Obstet Gynaecol 2024;32:278-86.
5. Polyota S, Tungmunsakulchai R, Tangsiriwatthana T. Comparison of the efficacy between conjugated equine estrogen versus nonsteroidal anti-inflammatory drug for the cessation of uterine bleeding among contraceptive implant users: A randomized controlled trial. Thai J Obstet Gynaecol 2024;32:287-94.
6. Achavangkool T, Wongwananuruk T, Hataiyusuk S, Chantrapnichkul P, Indhavivadhana S, Tanmahasamut P, et al. Prevalence of depressive symptoms among Thai reproductive-aged woman with polycystic ovary syndrome and associated factors. Thai J Obstet Gynaecol 2024;32:295-305.
7. Sangnucktham T, Bunyavejchevin S, Ruanphoo P. Validity and reliability of Thai version of the overactive bladder questionnaire short form in women with overactive bladder. Thai J Obstet Gynaecol 2024;32:306-13.
8. Horibe Y, Kanno T, Motohashi T, Akizawa Y, Funamoto H, Tabata T. Mesonephric-like adenocarcinoma arising from the ovary: A case review and treatment considerations. Thai J Obstet Gynaecol 2024;32:314-9.
9. Jayasakoon K, Pongrojpaw D, Punyashthira A, Sammor A, Chanthasenanont A, Suwannarurk K. Twin pregnancy presenting with hydatidiform mole and co-existing living fetus with ovarian venous thrombosis: A case report. Thai J Obstet Gynaecol 2024;32:320-7.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 257-260.

## SPECIAL ARTICLE

# Update on Amniocentesis

Jitti Hanprasertpong, M.D.*,
Tharangrut Hanprasertpong, M.D.**

** Department of Research and Medical Innovation, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand*
*** Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakornnayok, Thailand*

**ABSTRACT**

Amniocentesis is a common prenatal diagnostic procedure. All steps before, during and after the procedure are essential and should be carefully performed. Moreover, there are several interesting and update aspects. This article aims for updating of amniocentesis in pregnant women with specific conditions, such as those infected with human immunodeficiency virus (HIV), those taking antiplatelet medications (such as aspirin), those who are obese, those who are infected with hepatitis B, and those experiencing a twin pregnancy.

**Keywords:** amniocentesis, human immunodeficiency virus, obese, hepatitis B, twins.

***Correspondence to:*** *Tharangrut Hanprasertpong, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot university, Ongkharak, Nakornnayok 26120, Thailand. Email: tharangrut@hotmail.com; tharangrut@gmail.com*

**Received:** 12 June 2024, **Revised:** 17 June 2024, **Accepted:** 19 June 2024

## Introduction

Amniocentesis is a common prenatal diagnostic procedure. The amniotic fluid is transabdominally withdrawn from the gestational sac and used for diagnosis of abnormal fetal conditions. In Thailand, the procedure was first performed in the year 1978, aiming to evaluate the number of fetal chromosomes[1]. Currently, most amniocentesis procedures are performed under continuous ultrasonographic guidance and the complication-related amniocentesis rate in singleton pregnancies is approximately 0.1%[2]. All steps before, during and after the procedure are essential and should be carefully done, including patient and family counselling, patient preparation, the procedure itself, immediate and late post-procedural management and complication-related procedural monitoring. Initially, a reasonable indication must be provided for each individual pregnant woman. Common indications for amniocentesis are described as follows:[3]

1. A pregnant woman who has a high risk of abnormal fetal aneuploidy (trisomy 13, 18 or 21): The

risk may be found by analyzing maternal history or background risk (maternal age, previous child affected by aneuploidy), maternal serum assessment (first-trimester combined test, quadruple test), abnormal ultrasonographic fetal structures or positive non-invasive prenatal testing, etc.

2. A pregnant woman who has a high risk of having a fetus affected by a single-gene disorder such as thalassemia

3. Intrauterine infection diagnosis

4. Therapeutic relief of discomfort symptoms in a pregnant woman who is affected by polyhydramnios or therapeutic reduction of amniotic fluid in a pregnant woman with twin-to-twin transfusion syndrome

After the indication has been identified, the pregnant woman and her partner must be counselled about her individual amniocentesis indication. Partner involvement during antenatal counselling is preferred because our previous study found that a partner's involvement in antenatal genetic counselling resulted in a higher proportion of participants who increased their knowledge score when comparing the score prior to and immediately after antenatal genetic counselling[4]. With regard to counselling methods, several techniques were introduced, including group or individual counselling, reading leaflets by oneself and computer-assisted instruction. Our previous study found that both reading leaflets by oneself and computer-assisted instruction methods improved pregnant women's knowledge and satisfaction and reduced pain and anxiety. In combination with individual counseling, reading leaflets by oneself was more effective than computer-assisted instruction in improving pregnant women's knowledge before second-trimester genetic amniocentesis[5]. In any case, all pregnant women should be asked to provide informed consent before the procedure.

In our opinion, the most interesting issue in this update on amniocentesis is amniocentesis in pregnant women with specific conditions, such as those infected with human immunodeficiency virus (HIV), those taking antiplatelet medications (such as aspirin), those who are obese, those who are infected with hepatitis B, and those experiencing a twin pregnancy

## Amniocentesis for pregnant women infected with human immunodeficiency virus (HIV)

In the past, vertical HIV transmission has been reported at rates of around 15-40% without antiretroviral (ART) drugs[6], and amniocentesis was prohibited because of the concern that maternal blood exposure during amniocentesis may increase the risk of mother-to-child transmission[6]. However, the proper administration of highly active antiretroviral therapy (HAART) has led to an effective reduction of the viral load in both maternal blood and amniotic fluid[7]. Therefore, the recommendations for amniocentesis in HIV-positive women have changed. Most of the recent literature suggests that it is safe to perform amniocentesis in women on HAART with undetectable viral loads[8-9]. In the literature, rates of 0/20 and 1/7 vertical HIV transmission after amniocentesis with and without HAART therapy, respectively, have been reported[10]. However, placental injury should be avoided[8]. For HIV-positive women who are not undergoing HAART and have an unknown viral load, the procedure must be postponed[10]. In any case, in our practice, we still avoid amniocentesis in HIV-positive women as much as possible. Non-invasive prenatal investigation is more preferred because we believe that the number of reported cases may be not enough to warrant definite safety confirmation.

## Amniocentesis for pregnant women taking aspirin

The benefit of using daily low-dose aspirin from the late stages of the first trimester to prevent or delay the onset of preeclampsia has been proven and is widely accepted[11]. Therefore, some amniocentesis-indicated pregnant women will be taking low-dose aspirin, and concern about the potential risk of bleeding complications is warranted. Moreover, an increased risk of nonreportable cell-free DNA results in pregnant women taking low-dose aspirin has been reported[12]. Until now, there have been no studies or

case reports which have demonstrated that aspirin usage during amniocentesis is either safe or dangerous. There is no definite evidence that discontinuing aspirin before amniocentesis is clinically reasonable. In other minor procedures, aspirin discontinuation is done in a range of 5 to 7 days before the procedure (>10 days is too early; </= 3 days is too late)[13-14]. Our preference is to discuss the bleeding risk and thrombotic risk with the pregnant women. The management of the risk is decided together. If discontinuation is decided, doing it 5 to 7 days before the procedure is our suggestion.

### Amniocentesis for pregnant women who are obese

Obesity is a significant problem during pregnancy. In Europe, 20 to 40 percent of pregnant women excessively gained weight, beyond the recommended GWG, and were affected by additional obstetric complications[15]. The limitations of ultrasonographic image exposure and procedural technical difficulty are important aspects of concern. Gentle pressure on the abdominal wall to collapse the abdominal wall thickness accompanied with a special long spinal needle is our suggestion for easier passage through the amniotic sac. A maternal fetal medicine specialist should be consulted in the most difficult cases.

### Amniocentesis for pregnant women infected with hepatitis B

The overall vertical transmission rate of hepatitis B in pregnant women who have undergone amniocentesis is higher than the rate in pregnant women who have not undergone amniocentesis (6.35 vs. 2.53%)[16], especially in those with a high viral load (>/=7 log10 copies/mL) or positive HBe antigen[17]. Thus, the suggestion is to decrease the viral load and avoid placental injury during the needle puncture[18].

### Amniocentesis for women experiencing a twin pregnancy

The tendency of fetal loss after amniocentesis in twin pregnancies has been found to be higher than in singleton pregnancies. Our previous retrospective descriptive study reported that the rate of fetal loss within 14 days after second-trimester amniocentesis was 1.4%[19]. The important initial step before amniocentesis in twin pregnancies is chorionic determination. Then, decisions are made on the location of the puncture site and the number of sac punctures needed. In dichorionic twin pregnancies, sampling of both sacs is preferred. Indigo carmine may be injected into the first sac, allowing the operator to identify if the second sample is from the same sac or not[16].

In monochorionic, diamniotic twins, the number of sacs sampled depends on fetal anatomy and ultrasonographic evaluation of growth. Two-sac sampling may be indicated in cases of discordant fetal growth or anatomy[16].

## Conclusion

In conclusion, amniocentesis is a common prenatal invasive diagnosis. However, medical professionals should get up to date on several specific conditions due to recent scientific knowledge improvements.

## Potential conflicts of interest

The author declares no conflicts of interest.

### References


1. Hanprasertpong T, editor. Amniocentesis. Songkla. PP Media Design and print 2018:1-7.
2. Hanprasertpong T, Kor-anantakul O, Prasartwanakit V, Leetanaporn R, Suntharasaj T, Suwanrath C. Outcome of second trimester amniocentesis in singleton pregnancy at Songklanagarind hospital. J Med Assoc Thai 2011;94:1288-92.
3. Cunningham FG, Leveno KJ, Dashe JS, Hoffman BL, Spong CY, Casey BM. Williams Obstetrics. 26 th ed. New York: Mc Graw Hill 2022:332-51.
4. Anansirikasem T, Kongsomboon K, Hanprasertpong T. The influence of the partner's involvement in antenatal genetic group counseling on pregnant individuals' scores on tests of vital knowledge relating

to pregnancy. Am J Perinatol 2024;41(S 01):e1623-e1630.
5. Hanprasertpong T, Rattanaprueksachart R, Janwadee S, Geater A, Kor-anantakul O, Suwanrath C, Hanprasertpong J. Comparison of the effectiveness of different counseling methods before second trimester genetic amniocentesis in Thailand. Prenat Diagn 2013;33:1189-93.
6. Andany N, Letchumanan M, Bondy L, Murphy K, Loutfy MR. Amniocentesis in the HIV-infected pregnant woman: Is there still cause for concern in the era of combination antiretroviral therapy?. Can J Infect Dis Med Microbiol 2013;24:e91-5.
7. Maiques V, García-Tejedor A, Perales A, Córdoba J, Esteban RJ. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women?. Eur J Obstet Gynecol Reprod Biol 2003;108:137-41.
8. Constantatos SN, Boutall AH, Stewart CJ. Recommendations for amniocentesis in HIV-positive women. S Afr Med J 2014;104:844-5.
9. Simoes, M., Marques, C., Albergaria, F., Guerreiro C, Pereira A, Correia J, et al. Amniocentesis is a low-risk procedure in HIV-treated pregnant women. J Int AIDS Soc 2010;13(S 4):163.
10. Simões M, Marques C, Gonçalves A, Pereira AP, Correia J, Castela J, Guerreiro C. Amniocentesis in HIV pregnant women: 16 years of experience. Infect Dis Obstet Gynecol 2013;1:914272.
11. ACOG Committee Opinion No. 743: Low-dose aspirin use during pregnancy. Obstet Gynecol 2018;132: e44-e52
12. Nitsche JF, Lovell D, Stephens N, Conrad S, Bebeau K, Brost BC. The effects of heparin, aspirin, and maternal clinical factors on the rate of nonreportable cell-free DNA results: a retrospective cohort study. Am J Obstet Gynecol MFM 2023;5:100846.
13. Plümer L, Seiffert M, Punke MA, Kersten JF, Blankenberg S, Zöllner C, Petzoldt M. Aspirin Before Elective Surgery-Stop or Continue?. Dtsch Arztebl Int 2017;114:473-80.
14. Moster, M., Bolliger, D. Perioperative guidelines on antiplatelet and anticoagulant agents: 2022 update. Curr Anesthesiol Rep 2022;12:286-96.
15. Sareerat S, Kongsomboon K, Hanprasertpong T. Comparing the different antenatal nutritional counseling methods regarding proper gestational weight gain during the second trimester: A randomized, controlled trial. Thai J Obstet Gynaecol 2024;32;278-86.
16. Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z, McGillivray G; International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. Ultrasound Obstet Gynecol 2016;48:256-68.
17. Yi W, Pan CQ, Hao J, Hu Y, Liu M, Li L, Liang D. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol 2014;60:523-9.
18. Gagnon A, Davies G, Wilson RD; Genetics Committee. retired: Prenatal invasive procedures in women with hepatitis B, hepatitis C, and/or human immunodeficiency virus infections. J Obstet Gynaecol Can 2014;36: 648-53.
19. Hanprasertpong T, Kor-anantakul O, Prasartwanakit V, Leetanaporn R, Suntharasaj T, Suwanrath C. Outcome of second trimester amniocentesis in twin pregnancies at Songklanagarind Hospital. J Med Assoc Thai 2008;91:1639-43.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 261-268.

## GYNAECOLOGY

# A Comparison of Conventional Outpatient and Instrumental Intraoperative Pelvic Organ Prolapse Quantification Measurements in Patients Undergoing Vaginal Surgery for Pelvic Organ Prolapse

Kreaingsak Sirisakpanich, M.D.*,
Karmonpob Wechchasart, M.D.*

** Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand*

## ABSTRACT

**Objectives:** To compare the differences of pelvic organ prolapse quantification (POP-Q) measurements obtained preoperatively at the outpatient setting and intraoperatively with instrumental traction during full anesthetization in patients undergoing vaginal reconstructive surgery.

**Materials and Methods:** Retrospective chart review of 98 women having undergone vaginal pelvic organ prolapse (POP) repair for ≥ stage II uterovaginal prolapse during September 2014 and March 2020 at Phramongkutklao Hospital was conducted. Patients' baseline characteristics, history of POP and anti-incontinence surgery, clinical manifestations, POP stage, pessary use, and pre- and intra-operative POP-Q measurements were recorded. At preoperative outpatient setting, POP-Q examination was performed during maximal Valsalva. Intraoperatively, it was performed with instrumental cervical traction after full anesthetization. All POP-Q measurements were interpreted for prolapse location and severity according to the standardized POP-Q system.

**Results:** Mean age was 72.08 years, with 98% being postmenopausal. Mean body mass index (BMI) was 25.08 kg/m$^2$. Most had vaginal deliveries with a median parity of 3. All manifested with bulge symptom while 79.6% complained of voiding difficulty. 96 out of 98 presented with advanced stage prolapse. Among these, 20 patients were treated with vaginal pessary during the waiting period for POP surgical repair. POP-Q measurements (Ba, Ap, Bp, C, D, GH, and PB) obtained during intraoperative instrumental traction significantly demonstrated more prolapse severity when compared with those obtained during outpatient setting. No changes were found when evaluating point Aa

**Conclusion:** POP-Q measurements obtained during conventional outpatient examination provided less prolapse severity when compared with those measured during intraoperative instrumental traction after full anesthetization.

**Keywords:** pelvic organ prolapse, POP-Q examination, POP-Q measurement, outpatient, intraoperative.

***Correspondence to:*** *Kreaingsak Sirisakpanich, M.D., Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand. E-mail: suvit.b@chula.ac.th*

**Received:** 7 February 2023, **Revised:** 22 January 2024, **Accepted:** 8 March 2024

# *การเปรียบเทียบผลการตรวจหาตำแหน่งและระดับความรุนแรงของอวัยวะอุ้งเชิงกรานหย่อนด้วยมาตรวัดพอปคิว ระหว่างการตรวจด้วยวิธีมาตรฐานแบบผู้ป่วยนอกและการตรวจในห้องผ่าตัดภายหลังการระงับความรู้สึก ในผู้ป่วยที่มารับการผ่าตัดทางช่องคลอดรักษาอวัยวะอุ้งเชิงกรานหย่อน*

***เกรียงศักดิ์ ศิริศักดิ์พาณิชย์, กมลภพ เวชชศาสตร์***

## *บทคัดย่อ*

***วัตถุประสงค์****: เพื่อเปรียบเทียบผลการตรวจหาตำแหน่ง (location) และระดับความรุนแรง (stage)ของอวัยวะอุ้งเชิงกรานหย่อนด้วยมาตรวัดพอปคิว(POP-Q)ระหว่างการตรวจด้วยวิธีมาตรฐานแบบผู้ป่วยนอกและการตรวจในห้องผ่าตัดโดยใช้เครื่องมือช่วยดึงภายหลังการระงับความรู้สึก*

***วัสดุและวิธีการ****: ดำเนินการวิจัยแบบเก็บข้อมูลย้อนหลัง ที่กองสูตินรีเวชกรรม โรงพยาบาลพระมงกุฎเกล้าโดยทำการศึกษาในผู้ป่วยที่ได้รับการการผ่าตัดผ่านทางช่องคลอดด้วยภาวะอวัยวะในอุ้งเชิงกรานหย่อน ณ กองสูตินรีเวชกรรม โรงพยาบาลพระมงกุฎเกล้า ตั้งแต่เดือน กันยายน 2557 ถึง มีนาคม 2563*

***ผลการศึกษา****: การวัดพอปคิวทั้งเก้าจุดด้วยวิธีมาตรฐานแบบผู้ป่วยนอกและการตรวจในห้องผ่าตัดภายหลังการระงับความรู้สึก มีความสัมพันธ์กันอย่างมีนัยสำคัญโดยการใช้ Spearman rank correlation ค่าเฉลี่ยพอปคิวที่จุด Aa ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ระหว่างการตรวจด้วยวิธีมาตรฐานแบบผู้ป่วยนอกและการตรวจในห้องผ่าตัดภายหลังการระงับความรู้สึก (p = 0.611) ค่าพอปคิวที่จุด Ba แตกต่างอย่างมีนัยสำคัญทางสถิติ (p = 0.003) (ค่าเฉลี่ยของผลต่างเท่ากับ 0.52 เซนติเมตร) ระหว่างการตรวจด้วยวิธีมาตรฐานแบบผู้ป่วยนอกและการตรวจในห้องผ่าตัดภายหลังการระงับความรู้สึก (3.99±1.47 และ 4.51±1.81 เซนติเมตร) เช่นเดียวกับที่จุด C (p = 0.001) (ค่าเฉลี่ยของผลต่าง = 0.94 เซนติเมตร) ระยะโรคของภาวะอุ้งเชิงกรานหย่อนจากการตรวจทั้ง 2 วิธีพบว่ามีการพบระยะที่มากขึ้น ร้อยละ 19.39 (19/98) ยังคงระยะเดิม ร้อยละ 65.30 (64/98) และลดระยะลง ร้อยละ 15.30 (15/98)*

***สรุป****: การวัดพอปคิวด้วยการตรวจด้วยวิธีมาตรฐานแบบผู้ป่วยนอกอาจทำให้ได้ระยะและความรุนแรงของภาวะอุ้งเชิงกรานหย่อนน้อยกว่าการการตรวจในห้องผ่าตัดโดยใช้เครื่องมือช่วยดึงภายหลังการระงับความรู้สึก ผู้ป่วยที่ได้รับการวางแผนเพื่อผ่าตัดรักษาภาวะอุ้งเชิงกรานหย่อนควรได้ทราบว่าอาจมีการเปลี่ยนแปลงแผนการผ่าตัดจากที่ได้แจ้งไว้ก่อนล่วงหน้าที่จะผ่าตัด*

***คำสำคัญ****: อวัยวะอุ้งเชิงกรานหย่อน, มาตรวัดพอปคิว, เครื่องมือช่วยดึง*

## Introduction

Pelvic organ prolapse (POP) is a common problem among aging population worldwide that considerably impacts women's quality of life. Although accepted as a low mortality and morbidity condition, it is a usual indicator for vaginal reconstructive surgery[1], with the estimated 11% life-time risk of undergoing at least one POP or anti-incontinence surgery[2]. To specifically plan for surgical treatment option, the exact site and severity of prolapse should be preoperatively identified. This can be achieved using the standardized pelvic organ prolapse quantification (POP-Q) system which was developed and introduced by the International Continence Society (ICS) in 1996 to precisely measure and define POP stage and location[3]. However, several studies have demonstrated that POP-Q measurements obtained during strong cough or maximal Valsalva while patients being positioned in dorsal lithotomy at the outpatient setting show less prolapse severity than the measurements acquired using intraoperative instrumental traction while being fully anesthetized[4, 5]. Possible factors contributing to this underestimation of outpatient POP severity included full bladder, fear, embarrassment, pain, impacted feces, and pelvic floor muscle contraction. Consequently, this often led to change in the planned surgical procedures, from simple hysterectomy and colporrhaphy procedures to vaginal obliteration or sophisticated mesh augmentation procedures, thus requiring more informative and thorough preoperative counseling prior to undergoing POP repair. Therefore, the purpose of this study is to compare the differences of POP-Q measurements obtained preoperatively at the outpatient setting and intraoperatively with instrumental traction during full anesthetization in patients undergoing vaginal reconstructive surgery.

## Materials and Methods

Following the Institutional Review Board's ethical approval for the expedited-review research category, the retrospective study of all women undergoing vaginal reconstructive surgery for at least stage II uterovaginal prolapse during September 2014 and March 2020 at the Department of Obstetrics and Gynecology, Phramongkutklao General Hospital, was carried out. Patients' medical data including age, body mass index (BMI), parity, mode of delivery, menopausal status, previous POP and anti-incontinence surgery, clinical manifestations, POP stage, pessary use, as well as outpatient and intraoperative POP-Q measurements were thoroughly reviewed and recorded. Those with incomplete medical information were excluded from the study.

During the initial visit at the urogynecology outpatient clinic, patients were evaluated for presenting POP symptoms, as well as associated lower urinary tract (LUT) and defecatory symptoms. Following single catheterization to measure post-void residual urine, POP location and severity were assessed and interpreted during maximal Valsalva or strong cough while patients being positioned in dorsal lithotomy, according to the standardized POP-Q system[6]. The posterior blade of the Graves vaginal speculum was used to assess the most descending points on the anterior (point Aa, Ba) and posterior (point Ap, Bp) compartments separately. No speculum was used when evaluating for apical descent (point C, D). Total vaginal length (TVL) was measured without Valsalva maneuver. A POP ruler which was adapted from the modified Ayre's spatula, pre-marked with centimeter markings, was used to objectively quantify all POP-Q measurements. All six points (Aa, Ba, Ap, Bp, C, and D) were recorded in centimeters in relation to the hymen, with 0 if located at hymeneal ring, with negative values if located above hymen, and with positive values if located below hymen[6]. The three additional distances including genital hiatus (GH), perineal body (PB), and total vaginal length (TVL) were also recorded in centimeters without plus or minus symbols. After having obtained all POP-Q measurements, each patient was then assigned with POP stage, from 0 (no descent) to IV (complete protrusion), in regard to the most descending point of prolapse.

Women who underwent vaginal reconstructive surgery for at least stage II uterovaginal prolapse were reassessed for POP-Q measurements intraoperatively.

Following general or regional anesthesia, the patients were positioned in dorsal lithotomy with a 14-French Foley's catheter being inserted to continuously drain the bladder. POP-Q examination was performed under cervical traction using a Schroeder tenaculum forceps to gain maximal descent. POP-Q measurements, except TVL, were measured during this instrumental traction. Only one experienced urogynecologist (KS) was responsible for all surgical procedures and POP-Q examination.

***Sample size calculation***

According to the study by Krissi et al[7], who evaluated the preoperative and intraoperative POP-Q measurements in women undergoing vaginal reconstructive surgery for prolapse, the formula to compare two dependent means was applied for sample size calculation. With the preoperative and intraoperative point D of -4.2 (SD = 2.1) and -3.4 (SD = 2.5) respectively, the mean difference was 0.8. With the pre-defined values of (1) 95% confidence level (Z-alpha/2 = 1.96), (2) 90% power of detecting a difference ($Z\beta$ = 1.28), and (3) standard deviation of 2.1, the sample size was calculated to be 55. An extra 10% of the estimated samples were added to compensate for any missing data, thus yielding a total of at least 61 patients for the study.

$$N = \frac{(Z\alpha/2 + Z\beta)^2 \times (\sigma)^2}{(\Delta)^2}$$

***Statistical analysis***

The statistical analysis was performed using the Statistical Packages for the Social Sciences Version 23.0 for Windows (SPSS Inc, Chicago, IL, USA). The continuous variables were described as mean ± standard deviation (SD) or median (minimum-maximum) whereas the categorical data were expressed as number and percentage. The mean differences between preoperative and postoperative POP-Q values were compared using Wilcoxon Signed Ranks Test, whereas the correlation between the two methods was evaluated using the nonparametric Spearman Rank Correlation Test. A p value of less than 0.05 was considered as statistically significant.

# Results

With the exclusion of those with incomplete medical records, a total of 98 women who underwent vaginal reconstructive surgery for at least stage II uterovaginal prolapse were eligible and enrolled for this study. The mean age was 72.08 ± 8.57 years, with 98% being postmenopausal. The mean BMI was 25.08 ± 4.42 kg/m$^2$. Almost 90% had vaginal deliveries with the median parity of 3 (range 0-10). None had ever undergone surgery for POP and urinary incontinence, neither vaginally nor abdominally. All manifested with bulge symptom with voiding difficulty being the most common LUT complaint (79.6%). Constipation was found in only one-third of the patients (35.7%). Almost all (96 out of 98; 97.96%) presented with advanced stage (stage III and IV) prolapse. Among these, 20 patients (5 of stage III and 15 of stage IV) were treated with vaginal pessary to relieve bulge symptom and voiding difficulty during the waiting period prior to POP surgical repair (Table1).

All POP-Q measurements, both obtained pre- and intraoperatively, showed significant correlation (correlation coefficient 0.251 - 0.721; all $p < 0.05$). Of the six-point measurements measured during intraoperative instrumental traction, all except point Aa (Aa: 2.39 ± 0.86 vs 2.46 ± 0.92; p = 0.611) significantly demonstrated more prolapse severity when compared with those obtained during the outpatient setting. Pre- and intraoperative comparison of GH and PB distances also revealed significant changes towards more widening of genital hiatus and more flattening of perineal body when intraoperative cervical traction was applied during POP-Q examination (GH: 4.98 ± 0.95 vs 4.31 ± 1.10, $p < 0.001$ and PB: 3.35 ± 0.62 vs 3.61 ± 0.62, p = 0.001). Although total vaginal length was remarkably longer in terms of statistical analysis when measured intraoperatively during full anesthetization, there seemed to be no clinical significance (TVL: 7.77 ± 1.29 vs 7.18 ± 0.76, $p < 0.001$) (Table 2). Furthermore, the comparative outcomes between pre- and intraoperative POP-Q measurements were illustrated in Fig. 1 for better understanding.

**Table 1.** Patient demographics and clinical characteristics (n = 98).

| Characteristics | Values (n = 98) | |
|---|---|---|
| | n | % |
| Age (y) | | |
| < 60 | 7 | 7.1 |
| 60-69 | 22 | 22.4 |
| 70-79 | **55** | **56.1** |
| ≥ 80 | 14 | 14.3 |
| Mean ± SD | 72.08 ± 8.57 | |
| BMI (kg/m$^2$) | | |
| < 18.5 | 5 | 5.1 |
| 18.5-24.9 | 45 | 45.9 |
| 25-29.9 | 37 | 37.8 |
| ≥ 30 | 11 | 11.2 |
| Mean ± SD | 25.08 ± 4.42 | |
| Parity | | |
| 0 | 3 | 3.1 |
| 1 | 6 | 6.1 |
| 2 | 25 | 25.5 |
| 3 | 27 | 27.6 |
| ≥ 4 | 37 | 37.8 |
| Median (min - max) | 3 | 0 - 10 |
| Mode of delivery | | |
| NL | 84 | 88.4 |
| C/S | 11 | 11.6 |
| Menopause | 96 | 98.0 |
| POP symptom | | |
| Bulge | 98 | 100 |
| LUT symptom | | |
| No symptom | 13 | 13.3 |
| Void difficulty | 78 | 79.6 |
| OAB | 3 | 3.1 |
| SUI | 4 | 4.1 |
| Bowel symptom | | |
| No symptom | 63 | 64.3 |
| Constipation | 35 | 35.7 |
| POP stage | | |
| Stage II | 2 | 2.04 |
| Stage III | 51 | 52.04 |
| Stage IV | 45 | 45.92 |
| Pessary use | 20 | 20.4 |

Data were presented as mean ± SD, median (min-max), or number (%)

LUT: lower urinary tract, OAB: overactive bladder, SUI: stress urinary incontinence, SD: standard deviation, BMI: body mass index, NL: newborn length, C/S: cesarean section, POP: pelvic organ prolapse.

**Table 2.** Comparison of pre- and intraoperative POP-Q measurements (n = 98).

| POP-Q | Preoperative conventional | Intraoperative instrumental | Mean diff | 95% CI | | p value | Correlation coefficient (rs) | p value of correlation |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | | Lower | Upper | | | |
| Aa | 2.46 ± 0.92 | 2.39 ± 0.86 | 0.07 | -0.14 | 0.27 | 0.611 | 0.251 | 0.013* |
| Ba | 3.99 ± 1.47 | 4.51 ± 1.81 | -0.52 | -0.87 | -0.17 | 0.003* | 0.506 | < 0.001* |
| C | 5.09 ± 2.76 | 6.03 ± 2.48 | -0.94 | -1.48 | -0.41 | < 0.001* | 0.567 | < 0.001* |
| D | 2.07 ± 3.51 | 3.17 ± 2.88 | -1.10 | -1.66 | -0.53 | 0.001* | 0.639 | < 0.001* |
| Ap | 0.98 ± 2.06 | 1.69 ± 1.31 | -0.71 | -1.03 | -0.38 | < 0.001* | 0.626 | < 0.001* |
| Bp | 1.49 ± 2.90 | 2.54 ± 2.22 | -1.05 | -1.46 | -0.64 | < 0.001* | 0.721 | < 0.001* |
| Gh | 4.31 ± 1.10 | 4.98 ± 0.95 | -0.68 | -0.86 | -0.49 | < 0.001* | 0.574 | < 0.001* |
| Pb | 3.61 ± 0.62 | 3.35 ± 0.62 | 0.27 | 0.11 | 0.42 | 0.001* | 0.272 | 0.007* |
| TVL | 7.18 ± 0.76 | 7.77 ± 1.29 | -0.58 | -0.84 | -0.32 | < 0.001* | 0.294 | 0.003* |

Data were presented as mean ± SD; Statistical analysis: Wilcoxon Signed Ranks Test and Spearman rank correlation; * statistical significance
POP-Q: pelvic organ prolapse quantification, SD: standard deviation, CI: confidence interval, TVL: total vaginal length

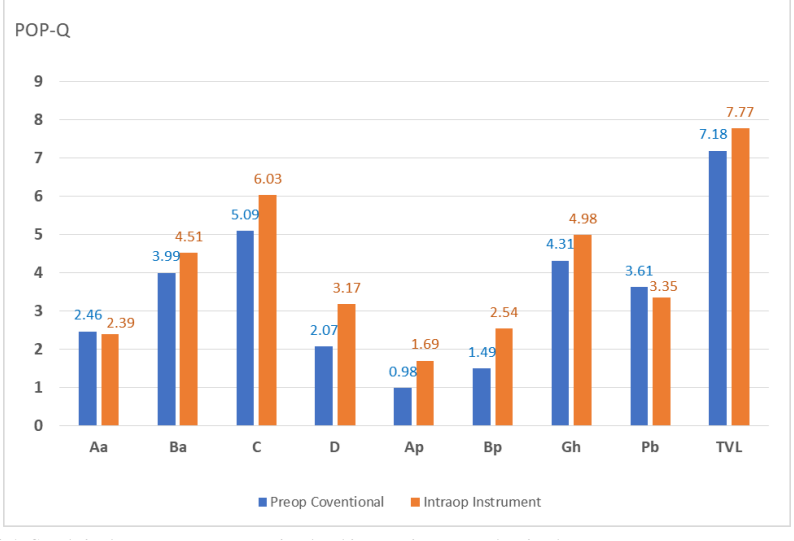


Fig. 1. Correlation between preoperative conventional and intraoperative instrumental assisted.
POP-Q: pelvic organ prolapse quantification, TVL: total vaginal length

When interpreting POP-Q measurements in terms of overall POP stage, two-thirds of the patients (64 out of 98; 65.30%) remained in the same stage, including 34 of stage III and 30 of stage IV, during intraoperative instrumental traction. Of the remaining one-third, 19 patients demonstrated up-staging while 15 patients down-staging (Table 3).

All patients underwent vaginal hysterectomy and concomitant procedures to correct the identifiable compartmental defects. Total colpocleisis was performed for non-sexually active women diagnosed intraoperatively with stage III-IV all-compartmental prolapse. High uterosacral vault suspension was conducted for those having at least stage II apical descent who wished to retain coital activity. Finally, anterior colporrhaphy and/or posterior colpoperineorrhaphy was carried out to correct cystocele and/or rectocele.

**Table 3.** Comparison of pre- and intraoperative POP stage (n = 98).

| | | Intraoperative instrumental | | Total |
|---|---|---|---|---|
| | | stage 3 | stage 4 | |
| Preoperative conventional | stage 2 | 0 (0) | 2 (2.04) | 2 (2.04) |
| | stage 3 | 34 (34.69) | 17 (17.35) | 51 (52.04) |
| | stage 4 | 15 (15.31) | 30 (30.61) | 45 (45.92) |
| Total | | 49 (50) | 49 (50) | 98 (100) |

POP: pelvic organ prolapse

# Discussion

Results from our study significantly demonstrated more prolapse severity in almost all POP-Q measurements (point Ba, Ap, Bp, C, D, GH, and PB) when POP-Q examination was performed using intraoperative cervical traction compared with the outpatient Valsalva maneuver. The findings corresponded with those of several previous studies[5, 7-8] which evaluated the outcomes of preoperative and intraoperative assessment of pelvic organ prolapse. Theoretically, this was possibly due to pelvic floor muscle relaxation which resulted from the blockage of pudendal nerve during general or regional anesthesia, leading to (1) reduced vaginal pressure, (2) increased width of urogenital hiatus, and (3) less resistive force to the prolapse on traction[9-11]. On the contrary, there was significant confounding effect of levator co-activation detected by 3D/4D ultrasound during the outpatient Valsalva technique, resulting in lesser extent of prolapse when inappropriate Valsalva was obtained during conventional POP-Q examination[12]. Hence, more attempts of proper and effective Valsalva are required to achieve maximal prolapse[13].

Although there was a significant correlation between point Aa values measured pre- and intraoperatively (correlation coefficient 0.251, p = 0.013), our study failed to demonstrate changes in Aa measurements (Aa: 2.39 ± 0.86 vs 2.46 ± 0.92; p = 0.611) when performing POP-Q examination under cervical traction. With the fixed urethral length and its distal end being embedded in the perineal membrane, point Aa which represents the location of the bladder neck, therefore, cannot be substantially pulled down during cervical traction, resulting in non-significant difference when compared between the two techniques.

When investigating in terms of overall POP stage, only 19.39% (19 out of 98) of the patients demonstrated more prolapse severity or up-staging during intraoperative POP-Q examination. This was similar to the result of Krissi et al[7] who reported increased stage in 12% of their study population. The explanation for this is that as many as 96 out of 98 recruited patients (97.96%) readily manifested with advanced stage prolapse, including 51 (52.04%) of stage III and 45 (45.92%) of stage IV. Hence, POP up staging during intraoperative instrumental traction could only be found in those previously diagnosed with stage II (2 out of 2) and stage III (17 out of 51) prolapse. Those preoperatively diagnosed with stage IV prolapse could either remain in stage IV (30 out of 45) or become demoted to stage III (15 out of 45). Preoperative use of vaginal pessary to relieve bulge symptom and voiding difficulty during the waiting period prior to reconstructive surgery may have provided partial pelvic support and be responsible for the unchanged and down-staging of prolapse when performing intraoperative POP-Q examination.

# Conclusion

POP-Q examination performed at the outpatient setting during strong cough or maximal Valsalva relatively provided less prolapse severity when evaluating in terms of POP-Q measurements (Ba, Ap, Bp, C, D, GH, and PB) compared with the examination

performed during intraoperative instrumental traction after full anesthetization. However, no significant difference was found when measuring point Aa. Therefore, patients diagnosed with pelvic organ prolapse who are scheduled for pelvic reconstructive surgery should be thoroughly counseled of all possible surgical options and be informed that the preoperatively planned surgical procedures may be opted or modified upon intraoperative POP-Q measurement outcomes.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References


1. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015;8:CD003677.
2. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501-5.
3. Bump RC, Matiason A, Bo K, Brubaker LP, DeLancey JOL, Klarskov P, et al. The standardization of terminology of female pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-7.
4. Vierhout ME, Stoutjesdijk J, Spruijt J. A comparison of preoperative and intraoperative evaluation of patients undergoing pelvic reconstructive surgery for pelvic organ prolapse using the pelvic organ prolapse quantification system. Int Urogynecol J 2005;17:46-9.
5. Doumouchtsis SK, Gauthamam N, Khunda A, Basu M, Dadhwal K, Gayle YV, et al. Comparison between the Valsalva maneuver and intraoperative traction measurements in pelvic organ prolapse assessment. Int J Gynaecol Obstet 2017;139:358-62.
6. Haylen BT, Maher CF, Barber MD, Camargo S, Dandolu V, Digesu A, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). Int Urogynecol J 2016;27: 655-84.
7. Krissi H, Eitan R, Ram E, Peled Y. How accurate is preoperative evaluation of pelvic organ prolapse in women undergoing vaginal reconstruction surgery? PLoS One 2012;7:e47027.
8. Vineyard DD, Kuehl TJ, Coates KW, Shull BL. A comparison of preoperative and intraoperative evaluation for patients who undergo site-specific operation for the correction of pelvic organ prolapse. Am J Obstet Gynecol 2002;186:1155-9.
9. Brazell HD, Claydon CS, Li J, Moore C, Dereska N, Hudson S, et al. Does neuromuscular blockade affect the assessment of pelvic organ prolapse? Int Urogynecol J 2012;23:1599-603.
10. Haeusler G, Sam G, Chiari A, Tempfer C, Hanzal E, Koelbl H. Effect of spinal anesthesia on the lower urinary tract in continent women. Br J Obstet Gynecol 1998;105:103-6.
11. Guaderrama NM, Liu J, Nager CW, Pretorius DH, Sheean G, Kassab G, et al. Evidence for the innervation of pelvic floor muscles by the pudendal nerve. Obstet Gynecol 2005;106:774-81.
12. Orno AK, Dietz HP. Levator co-activation is a significant confounder of pelvic organ descent on Valsalva maneuver. Ultrasound Obstet Gynecol 2007;30: 346-50.
13. Tumbarello JA, Hsu Y, Lewicky-Gaupp C, Rohrer S, DeLancey JO. Do repetitive Valsalva maneuver change maximum prolapse on dynamic MRI? Int Urogynecol J 2010;21:1247-51.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 269-277.

## OBSTETRICS

# Accuracy of the Combined First Trimester Down Syndrome Screening Test and the Optimum Range of the Cut-off Point for Intermediate-risk Identification: Twelve years' experience

Thanapa Rekhawasin Pinnington, M.D.*,
Jenjira Arthan, M.Sc.IT*,
Chulaluk Komoltri, DrPH**,
Pharuhas Chanprapaph, M.D.*

** Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thaland*
*** Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thaland*

## ABSTRACT

**Objectives:** This study aimed to determine the performance of the combined first trimester Down syndrome screening test and the appropriate cut-off points for intermediate-risk identification.

**Materials and Methods:** This was a retrospective study conducted from May 2019 to May 2021. All the medical charts of women with singleton pregnancy who had a first-trimester combined screening test performed between 2007 - 2018 were reviewed. A total of 3,928 women with singleton pregnancy were included in the final analysis. Data regarding neonatal outcomes were recorded, and a telephone follow-up was performed with the women who had given birth elsewhere. Statistical analysis was performed using SPSS version 18.0 software.

**Results:** With a high-risk cut-off point of 1:250, the test had a sensitivity of 75%, and a specificity and accuracy of 94%. When an intermediate-risk cut-off point between 1:500 and 1:1,000 was applied, the specificity and accuracy increased to 83% - 90%. When using a cut-off point between 1:251 and 1:1,000, the specificity and accuracy was 83%, while the rate of intermediate risk was 11.6%.

**Conclusion:** Our combined first-trimester screening test had a detection rate of 75%, and a high specificity and accuracy of 94%. The recommended cut-off point for intermediate risk was between 1:251 and 1:1,000, since this offered good specificity and accuracy with an acceptable rate of intermediate risk.

**Keywords:** combined first-trimester, cut-off point, Down syndrome, intermediate risk, screening.

***Correspondence to:*** *Pharuhas Chanprapaph, M.D., Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. E-mail: pharuhasc@gmail.com*

**Received:** 25 August 2023, **Revised:** 17 January 2024, **Accepted:** 23 February 2024

# *ความถูกต้องของการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม ในระยะเวลา 12 ปี*

***ธนาภา เรขาวศิน พินนิงตัน, เจนจิรา อาจหาญ, จุฬาลักษณ์ โกมลตรี, พฤหัส จันทร์ประภาพ***

## *บทคัดย่อ*

***วัตถุประสงค์****: เพื่อศึกษาความถูกต้องของการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม (combined first-trimester screening test) ในการทำนายทารกกลุ่มอาการดาวน์ในสตรีตั้งครรภ์*

***วัสดุและวิธีการ****: งานวิจัยนี้เป็นการศึกษาแบบย้อนหลัง โดยทำการศึกษาข้อมูลจากเวชระเบียนของสตรีตั้งครรภ์เดี่ยวที่มารับการตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสมในช่วงปี พ.ศ.2550-2561 จำนวน 3,928 ราย และติดตามข้อมูลการเกิดกลุ่มอาการดาวน์ของทารกแรกเกิด สำหรับสตรีตั้งครรภ์ที่ไม่ได้คลอดที่โรงพยาบาลศิริราช จะทำการโทรศัพท์เพื่อสอบถามข้อมูลทารกแรกเกิด*

***ผลการศึกษา****: ค่าจุดตัดที่บ่งชี้ภาวะความเสี่ยงสูงของการตรวจคัดกรองที่ 1:250 พบว่ามีความไวร้อยละ 75 ความจำเพาะและความแม่นยำ ร้อยละ 94 เมื่อพิจารณาช่วงค่าความเสี่ยงที่ใช้เพื่อบ่งชี้ภาวะความเสี่ยงปานกลาง (intermediate risk range) ระหว่าง 1:500 และ 1:1,000 พบว่ามีค่าความจำเพาะและความแม่นยำร้อยละ 83-90 สำหรับค่าจุดตัดในช่วง 1:251 ถึง 1:1,000 พบว่ามีความจำเพาะและความแม่นยำร้อยละ 83 และอัตราการตรวจพบความเสี่ยงปานกลางคิดเป็นร้อยละ 11.6*

***สรุป****: การตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสมมีค่าความไวร้อยละ 75 ความจำเพาะและความแม่นยำร้อยละ 94 โดยช่วงค่าความเสี่ยงที่แนะนำเพื่อบ่งชี้ภาวะความเสี่ยงปานกลางคือ 1:251 ถึง 1:1,000 เนื่องจากค่าจุดตัดดังกล่าวมีค่าความจำเพาะและความแม่นยำที่สูง และมีอัตราการตรวจพบความเสี่ยงปานกลางที่ยอมรับได้*

***คำสำคัญ****: การตรวจคัดกรองทารกกลุ่มอาการดาวน์ในไตรมาสแรกแบบผสม, ค่าจุดตัด, กลุ่มอาการดาวน์, ความเสี่ยงปานกลาง, การตรวจคัดกรอง*

## Introduction

Down syndrome is the most common autosomal aneuploidy and the cause of inherited intellectual disability, with an incidence of about 1 in 800 live births[1]. In Thailand, the incidence was reported to be 1.21 per 1,000 births[2]. Affected children can present with abnormal facial features, learning disorder, seizure, congenital heart disease, bowel atresia, leukemia, and a shorter life expectancy[1]. This syndrome can be found in all pregnant women, with a higher risk with increasing maternal age.

Screening for Down syndrome has been applied in clinical practice for over a half-century now, with various methods available. The first-trimester combined test, consisting of maternal age, nuchal translucency (NT) measurement, serum free beta-hCG (human chorionic gonadotropin), and PAPP-A (pregnancy-associated plasma protein-A), is one of the methods producing a high detection rate of more than 80%1, 3-10. However, the test results cannot be compared among studies and should be interpreted individually since some factors, including various ethnicities, cut-offs, and laboratory techniques, are influential in the results. Asian women were reported to have significantly different levels of serum free beta-hCG and PAPP-A, when compared with Caucasian women[11-15]. However, the serum level inclinations were even intriguingly found to be dissimilar between northern and southern parts of Thailand[14, 15].

Accordingly, the primary objective of this study was to determine the detection rate of the first-trimester combined test for Down syndrome screening at Siriraj Hospital, while the secondary objectives were to figure out a proper cut-off point for intermediate-risk identification and to identify the factors affecting the test accuracy.

## Materials and Methods

According to the study of Luo et al[16], the sensitivity and the specificity of the combined first trimester screening test was 78.79% and 98.41%, respectively. Assuming that the test accuracy was 90%, the calculated sample size should be at least 3,458 based on the 95% CI of 90% ± 1%.

This retrospective study was conducted at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University during May 2019 to May 2021. It was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 344/2019). All the medical charts of pregnant women who had the first-trimester combined screening test performed between 2007 - 2018 were reviewed. Women with singleton pregnancy and who had the first-trimester combined screening test were included in the study, and their neonatal outcomes were recorded. Telephone follow-up was performed to inquire about such information for the pregnant women who had given birth elsewhere. The women whose pregnancy outcomes could not be followed up were excluded.

***Outcome measures***

First-trimester screening was performed between $11^{+0}$ and $13^{+6}$ weeks of gestation at the Maternal Fetal Medicine Unit, where blood samples were also drawn. Gestational age was calculated based on either certain last menstrual period or the crown rump length (CRL). Nuchal translucency (NT) and CRL were measured by maternal fetal medicine (MFM) experts following the standard protocol of the Fetal Medicine Foundation (https://fetalmedicine.org/education/the-11-13-weeks-scan three times, and the widest value was used. If nuchal translucency was ≥ 3 mm, then a prenatal diagnostic test was offered. Biochemistry markers, including both serum free beta-hCG and PAPP-A, were measured using the Kryptor analyzer (Brahms AG, Berlin, Germany) and reported by the Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, whose laboratory has been accredited to a high international standard level with the receipt of ISO

15189 accreditation.

In our practice, the risk from the combined test was calculated and classified into high, intermediate and low risk. In this study, the cut-off limit of 1:250 was used to define high risk, 1:1,500 for low risk, and a value between 1:250 and 1:1,500 was classified as intermediate risk. For intermediate-risk and high-risk results, the pregnant women would receive counseling about the risks and benefits of both cell-free DNA screening and amniocentesis. They were allowed to choose either a prenatal test or postnatal evaluation.

To determine the most optimal range for the intermediate-risk group identification, we gradually lowered the cut-off point from 1:300 to 1:1,500. The test performances from each cut-off point (1:251-1:300, 1:251-1:400, 1:251-1:500, 1:251-1:600, 1:251-1:700, 1:251-1:800, 1:251-1:900, 1:251-1:1,000 and 1:251-1:1,500) were then compared and analyzed to obtain the best result.

The main outcome of interest was the number of newborns with Down syndrome who were identified by either prenatal amniocentesis or postnatal clinical diagnosis. The data of which were extracted from the electronic-based medical records. For women giving birth elsewhere than Siriraj Hospital, a telephone follow-up was made to ask about postnatal outcomes.

### *Statistical analysis*

Descriptive statistics were used as appropriate, including N (%), mean ± standard deviation (SD), and median with interquartile range (IQR). The chi square test was used for comparison of the categorical variables. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

## Results

During the study period, 4,006 pregnant women were identified as having had a combined first trimester Down syndrome screening test. There were 78 cases excluded from the study due to twin pregnancy with the remaining 3,928 singleton pregnancies.

From Table 1, it can be seen that the mean age and body mass index were significantly higher in the high-risk group. Regarding the biochemical markers, PAPP-A was significantly lower, 3,981.86 ± 4,684.37 vs. 5,799.47± 4,489.09 mIU/L, and free beta-hCG was significantly higher, 97.62 ± 65.32 vs. 52.14 ± 36.37 ng/mL, in the high-risk group. Nuchal translucency was also obviously higher in the high-risk group: 1.98 ± 0.69 vs 1.43 ± 0.46 mm. Intriguingly, the mean value for the combined risk of Down syndrome in the high-risk group was about 10 times higher than that in the low-risk group (1:124.19 vs 1: 13,169.53). Around 85% (182 out of 213) of the patients in the high-risk group and 15% (99 out of 660) in the intermediate-risk group opted to undergo a prenatal diagnostic (PND) procedure, whereas only 1.04% (32 out of 3,055) did so in the low-risk group.

There were 4 affected fetuses with trisomy 21 (T21) in this study, as confirmed by amniocentesis and postnatal outcome, with 3 of these in the high-risk group, while the remaining case was in the intermediate-risk group. All 4 of the pregnant women agreed to have an abortion after knowing the result, and the procedures went off without any complications. There was one affected fetus with trisomy 13 diagnosed by amniocentesis and abortion was also accomplished without any consequence.

The flow diagram showing the overall outcomes of all screening cases were shown in Fig. 1. Applying an original threshold of ≥1:250, 3,715 pregnant women were classified into the low-risk category. Among them, 131 individuals opted for prenatal invasive testing. Within this group, 99 and 32 pregnant women fell into

the intermediate and low-risk groups using the cut-off point at 1:251–1:1,500 and <1:1,500, respectively. Despite being aware of the procedural risks, they autonomously chose to undergo the invasive test for result confirmation. According to our unpublished data, factors positively influencing maternal decision-making to obtain prenatal diagnosis (PND) included a high monthly income, and primigravida women. Nevertheless, it is noteworthy that all women who refused PND in this study eventually delivered normal babies.

Using a cut-off point of ≥1:250 for high-risk identification, the efficacy of the test was demonstrated, including a sensitivity of 75%, negative predictive value (NPV) of 99.97%, and negative likelihood ratio of 0.26 (Table 2).

**Table 1.** Demographic data of the low-risk and high-risk groups (cut-off point ≥1:250).

| Data | Total | Low risk | High risk | p-value |
|---|---|---|---|---|
| | (N = 3,928) | (N = 3,715) | (N = 213) | |
| Maternal age[#] (years) | 31.01 ± 3.94 (15–46) | 30.86 ± 3.86 (15–46) | 33.63 ± 4.46 (21–44) | 0.00* |
| Body mass index[#] (kg/m$^2$) | 21.67 ± 3.82 (12.02–52.16) | 21.60 ± 3.72 (12.02–48.44) | 22.96 ± 5.14 (16.23–52.16) | 0.00* |
| GA by U/S[#] (days) | 87.55 ± 5.13 (61–98) | 87.50 ± 5.13 (61–98) | 88.48 ± 5.14 (72–97) | 0.01* |
| PAPP-A[$] (mIU/L) | 4,774 (2,985–7,257.75) | 4,887 (3,075–7,396) | 3,005 (1,518–4,856) | 0.00* |
| PAPP-A[$] (MoM) | 1.07 (0.72–1.54) | 1.09 (0.74–1.57) | 0.68 (0.41–1.05) | 0.00* |
| Free beta-hCG[$] (ng/mL) | 44.14 (29.10-67.62) | 42.75 (28.40–64.09) | 79.28 (54.45–121.90) | 0.00* |
| Free beta-hCG[$] (MoM) | 1.09 (0.74–1.66) | 1.06 (0.73–1.57) | 2.21 (1.43–3.25) | 0.00* |
| Nuchal translucency[$] (mm) | 1.40 (1.10–1.76) | 1.40 (1.10–1.70) | 1.90 (1.59–2.40) | 0.00* |
| Refusal of PND | 3,615 (92.0%) | 3,584 (96.5%) | 31 (14.6%) | 0.00** |
| Acceptance of PND | 313 (7.97%) | 131 (3.5%) | 182 (85.45%) | |
| - Chorionic villus sampling | 6 | 1 | 5 | |
| - Amniocentesis | 307 | 130 | 177 | |
| Fetal karyotype | | | | |
| - Trisomy 21 | 4 | 1 | 3 | |
| - Trisomy 13 | 1 | 1 | - | |
| - 46,XY,inv(9)(p12q13) | 2 | 2 | - | |
| - Other chromosomal abnormalities | 6 | 1 | 5 | |

[#] Data were shown in mean ± standard deviation (min-max), [$] Data were shown in median (interquartile range)

* Mann-Whitney U test, **Chi square test

GA: gestational age, U/S: ultrasound, PAPP-A: pregnancy-associated plasma protein A, hCG: human chorionic gonadotropin, MoM: multiples of the median, PND: prenatal diagnosis

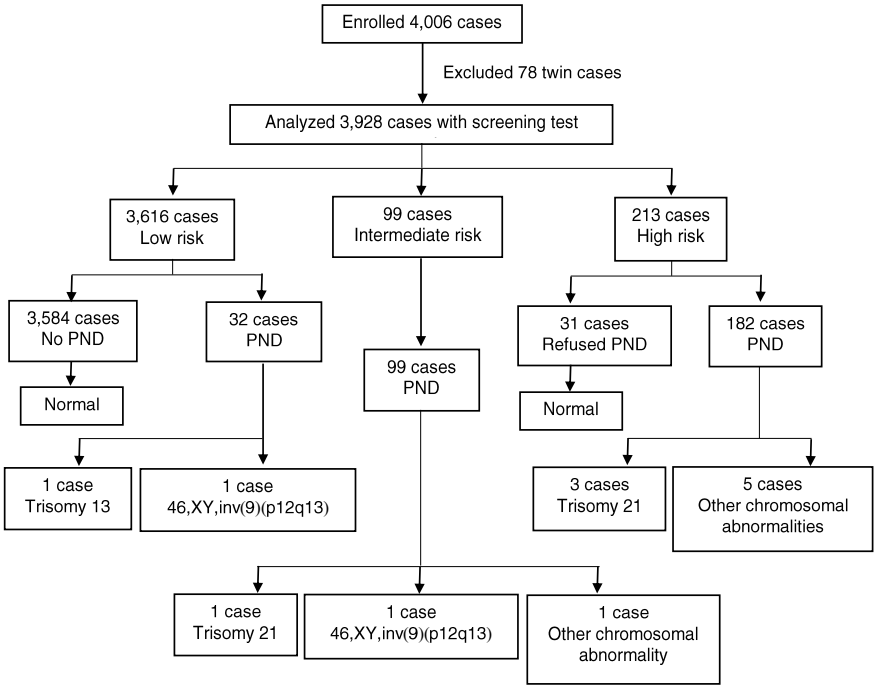


Fig. 1. Flow diagram showing the overall outcomes of all screening cases.
PND: prenatal diagnosis

**Table 2.** Efficacy of first trimester Down syndrome screening test in singleton pregnancy (n = 3,928) (cut-off point ≥ 1:250).

| Efficacy | Percentage | 95% CI (%) |
|---|---|---|
| Sensitivity | 75.0 | 19.41–99.37 |
| Specificity | 94.65 | 93.69–95.33 |
| Positive predictive value | 1.41 | 0.79–2.49 |
| Negative predictive value | 99.97 | 99.85–100 |
| Positive likelihood ratio | 14.01 | 7.84–25.05 |
| Negative likelihood ratio | 0.26 | 0.05–1.44 |
| Accuracy | 94.63 | 93.88–95.31 |

CI: confidence interval.

The test performance results for each intermediate risk range, defined by different cut-off points, were shown in Table 3, where it can be seen that the higher the cut-off point, the better the specificity and accuracy of the test. More than 90% specificity and accuracy were reported when the cut-off point of ≥1:400 was used, 83% - 90% of which was observed between the cut-off points of 1:500 to 1:1,000. The test performance was significantly lower when the cut-off point of 1:1,500 was used. When the cut-off point was ≥ 1:250, the incidence of positive screening tests was 5.42% (213/3,928) in this study. When using a risk of 1:251 to 1:1,500 for the determination, 16.8% (660 out of 3,928) of the patients with intermediate risk could be identified.

**Table 3.** Range of intermediate risk and number of cases needing to be consulted.

| Range of intermediate risk | Number of cases needing to be consulted | Specificity (%) | Accuracy (%) |
|---|---|---|---|
| 1:251–1:300 | 42 (1.07%) | 93.58 | 93.58 |
| 1:251–1:400 | 98 (2.49%) | 92.18 | 92.18 |
| 1:251–1:500 | 163 (4.15%) | 89.99 | 90.0 |
| 1:251–1:600 | 226 (5.75%) | 88.91 | 88.93 |
| 1:251–1:700 | 278 (7.07%) | 87.59 | 87.6 |
| 1:251–1:800 | 331 (8.42%) | 86.24 | 86.25 |
| 1:251–1:900 | 390 (9.92%) | 84.73 | 84.75 |
| 1:251–1:1,000 | 456 (11.6%) | 83.05 | 83.07 |
| 1:251–1:1,500 | 660 (16.8%) | 77.85 | 77.88 |

# Discussion

This study found a prevalence of Down syndrome of 0.10%, which was similar to in other studies conducted in the northern (0.14%) and southern (0.12%) parts of Thailand. Taking a high-risk test result into consideration, we found that a combined first-trimester test was effective for Down syndrome screening, with a sensitivity of 75%, and specificity and accuracy as high as 94%. The sensitivity or detection rate was lower in this study when compared with previous studies[5, 6, 17, 18], which could be due to the lower cut-off point of 1:150 used in some studies[17, 18], and the higher maternal age in others[5, 19]. Nonetheless, various cut-off points for classifying high-risk results could merely be taken into account in this study, since there were only a few cases of fetal Down syndrome.

In this study, we also aimed to evaluate pregnant women with an intermediate-risk result, because this can give rise to a secondary screening test as a non-invasive prenatal test (NIPT) or even unnecessary amniocentesis, potentially leading to fetal loss. Based on our current intermediate risk range of 1:251 - 1:1,500, the rate of detection was 16.8%, which was just slightly higher than the 14% rate for standard contingent screening[20]. Various lower cut-off points were studied to determine the range of intermediate risk that would provide for a proper efficacy of the test.

Charoenratana et al[20] and Gil et al[21], reported higher sensitivities (88.9% and 87%); however, the performances in their studies were less than in our study as the rates of intermediate risk in both studies were even higher than in ours (38.2% and 30.4%), and their upper cut-off point was much lower than in ours (1:30 vs. 1:100), and therefore, cases of fetal Down syndrome were more likely to be included in such a wider range. Moreover, the nuchal translucency value was not included in interpreting the risk of Down syndrome screening in the former study, and thereby, the sensitivity of the test could be deemed to be lower.

When compared with the results in the study by Guanciali-Franchi et al[3], who reported a slightly better performance, as their rate of intermediate risk was 12%, and their sensitivity was higher than in our study, 93% vs. 75 %, and this could result from the much higher value of the upper cut-off point of 1:30 in this study and the higher mean maternal age, 32.4 vs. 31 years old.

Luo et al[16], using an upper cut-off point of 1:270 and a lower cut-off point of 1:1,000, reported a better performance than in our study, as their rate of intermediate risk was only 3.37%, and the efficacy of the test was also better than in our study, as follows: sensitivity 78.79%, specificity 98.41%, and positive predictive value 7.03%. Nonetheless, we could not

perform a direct comparison with this study since the median serum levels of the biomarkers have been found to be dissimilar in different ethnic groups, even among Asian populations.

We performed analysis regarding different lower cut-off points for intermediate risk to find out the proper specificity and accuracy of the test, as shown in Table 2. Despite the intermediate-risk range of 1:251 to 1,500 previously used in this study, the recommended optimal range should be 1:251 to 1:1,000, since this would provide an adequate range with great specificity and accuracy of 83%. Evidently, the latter value could reduce the rate of the intermediate-risk group from 16.8% to 11.6%, which would not exceed the standard rate in contingent screening and could avoid the need for an unnecessary invasive prenatal test.

Some studies have reported that pregnant women with an increased fetal NT of more than 3.0–3.5 mm have been convinced to undergo an invasive prenatal diagnosis, either chorionic villus sampling or amniocentesis, with a chromosomal microarray study[22, 23]. Considering fetuses with an NT of > 3.5 mm in this study, there were 7 cases observed and none of them were affected with Down syndrome, while 25 pregnant women with a fetal NT of ≥ 3 mm were found, with only one fetal trisomy 21 case detected according to the amniocentesis result following a high-risk combined test result. There was only 4% of trisomy 21 cases among the fetuses with an NT of ≥ 3 mm in our study, which was lower than the level of 8.62% (5/58) reported in a previous study[24], raising a question regarding the necessity of undergoing amniocentesis just to confirm the fetal condition of Down syndrome. Our previous study also demonstrated that using increased NT as a single marker could detect fetal trisomy 21 with a sensitivity of 50.0 % and specificity of 91.94 %, respectively[25].

There are some limitations of this study to note, such as the data were collected retrospectively, and hence some selection bias was unavoidable. Moreover, a larger sample size would be required in order to be able to analyze what the appropriate upper cut-off point should be for combined first-trimester Down syndrome screening as only a few cases were found in this retrospective study.

This study also had some strengths to note that some other studies might not, since all the serum tests were analyzed in the same certified laboratory and the NT measurements were conducted by MFM specialists in a single tertiary center hospital. Therefore, variations in the population and test results could be less when compared with performing studies among various centers.

## Conclusion

Combined first-trimester screening, using a cut-off point of 1:250, provided great efficacy with a detection rate of 75 %, and specificity and accuracy of 94 %. Regarding the appropriate cut-off point for intermediate risk, we recommend a proper range of 1:251 to 1:1,000 as this elicited an acceptable rate of intermediate risk and a high specificity and accuracy of 83%.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References


1. Committee on Practice Bulletins-Obstetrics CoG, the Society for Maternal-Fetal M. Practice Bulletin No. 163: Screening for fetal aneuploidy. Obstet Gynecol 2016;127:e123-37.
2. Jaruratanasirikul S, Kor-Anantakul O, Chowvichian M, Limpitikul W, Dissaneevate P, Intharasangkanawin N, et al. A population-based study of prevalence of Down syndrome in Southern Thailand. World J Pediatr 2017;13:63-9.
3. Guanciali-Franchi P, Iezzi I, Soranno A, de Volo CP, Alfonsi M, Calabrese G, et al. Optimal cut-offs for Down syndrome contingent screening in a population of 10,156 pregnant women. Prenat Diagn 2012;32: 1147-50.
4. Crossley JA, Aitken DA, Cameron AD, McBride E, Connor JM. Combined ultrasound and biochemical screening for Down's syndrome in the first trimester: a Scottish multicentre study. BJOG 2002;109:667-76.
5. Lan RY, Chou CT, Wang PH, Chen RC, Hsiao CH. Trisomy 21 screening based on first and second trimester in a Taiwanese population. Taiwan J Obstet

Gynecol 2018;57:551-4.
6. Maxwell S, James I, Dickinson JE, O'Leary P. First trimester screening cut-offs for noninvasive prenatal testing as a contingent screen: Balancing detection and screen-positive rates for trisomy 21. Aust N Z J Obstet Gynaecol 2016;56:29-35.
7. Park SY, Jang IA, Lee MA, Kim YJ, Chun SH, Park MH. Screening for chromosomal abnormalities using combined test in the first trimester of pregnancy. Obstet Gynecol Sci 2016;59:357-66.
8. Schielen PC, Wildschut HI, Loeber JG. Down syndrome screening: determining the cutoff level of risk for invasive testing. Prenat Diagn 2009;29:190-2.
9. Soergel P, Pruggmayer M, Schwerdtfeger R, Muhlhaus K, Scharf A. Screening for trisomy 21 with maternal age, fetal nuchal translucency and maternal serum biochemistry at 11-14 weeks: a regional experience from Germany. Fetal Diagn Ther 2006;21:264-8.
10. Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003;110:281-6.
11. Manotaya S, Zitzler J, Li X, Wibowo N, Pham TM, Kang MS, et al. Effect of ethnicity on first trimester biomarkers for combined trisomy 21 screening: results from a multicenter study in six Asian countries. Prenat Diagn 2015;35:735-40.
12. Spencer K, Ong CY, Liao AW, Nicolaides KH. The influence of ethnic origin on first trimester biochemical markers of chromosomal abnormalities. Prenat Diagn 2000;20:491-4.
13. Leung TY, Spencer K, Leung TN, Fung TY, Lau TK. Higher median levels of free beta-hCG and PAPP-A in the first trimester of pregnancy in a Chinese ethnic group. Implication for first trimester combined screening for Down's syndrome in the Chinese population. Fetal Diagn Ther 2006;21:140-3.
14. Luewan S, Sirichotiyakul S, Yanase Y, Traisrisilp K, Tongsong T. Median levels of serum biomarkers of fetal Down syndrome detected during the first trimester among pregnant Thai women. Int J Gynaecol Obstet 2012;117:140-3.
15. Kor-Anantakul O, Suntharasaj T, Suwanrath C, Hanprasertpong T, Pranpanus S, Pruksanusak N, et al. Normative weight-adjusted models for the median levels of first trimester serum biomarkers for trisomy 21 screening in a specific ethnicity. PLoS One 2017;12:e0182538.
16. Luo W, He B, Han D, Yuan L, Chen X, Pang L, et al. A retrospective analysis of different contingent screening models for fetal Down syndrome In southwestern China. Sci Rep 2020;10:9457.
17. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med 2005;353:2001-11.
18. Santorum M, Wright D, Syngelaki A, Karagioti N, Nicolaides KH. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. Ultrasound Obstet Gynecol 2017;49:714-20.
19. Li SW, Barrett AN, Gole L, Tan WC, Biswas A, Tan HK, et al. The assessment of combined first trimester screening in women of advanced maternal age in an Asian cohort. Singapore Med J 2015;56:47-52.
20. Charoenratana C, Wanapirak C, Sirichotiyakul S, Tongprasert F, Srisupundit K, Luewan S, et al. Optimal risk cut-offs for Down syndrome contingent maternal serum screening. J Matern Fetal Neonatal Med 2018;31:3009-13.
21. Gil MM, Revello R, Poon LC, Akolekar R, Nicolaides KH. Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test. Ultrasound Obstet Gynecol 2016;47:45-52.
22. Schmid M, Klaritsch P, Arzt W, Burkhardt T, Duba HC, Hausler M, et al. Cell-Free DNA testing for fetal chromosomal anomalies in clinical practice: Austrian-German-Swiss Recommendations for non-invasive prenatal tests (NIPT). Ultraschall Med 2015;36: 507-10.
23. Lund IC, Christensen R, Petersen OB, Vogel I, Vestergaard EM. Chromosomal microarray in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol 2015;45:95-100.
24. Yoshida S, Miura K, Yamasaki K, Miura S, Shimada T, Tanigawa T, et al. Does increased nuchal translucency indicate a fetal abnormality? A retrospective study to clarify the clinical significance of nuchal translucency in Japan J Hum Genet 2008;53:688-93.
25. Chanprapaph P, Dulyakasem C, Phattanchindakun B. Sensitivity of multiple first trimester sonomarkers in fetal aneuploidy detection. J Perinat Med 2015;43: 359-65.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 278-286.

## OBSTETRICS

# Comparing the Different Antenatal Nutritional Counseling Methods Regarding Proper Gestational Weight Gain during the Second Trimester: A randomized, controlled trial

Sukanya Sareerat, M.D.*,
Kittipong Kongsomboon, M.D., PhD**,
Tharangrut Hanprasertpong, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Nakornnayok, Thailand*
*** Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Nakornnayok, Thailand*

## ABSTRACT

**Objectives:** To compare the two different antenatal nutritional counseling styles [computer-assisted instruction (CAI) and routine, casual, individual (RCI)] regarding the proper gestational weight gain (GWG) of healthy pregnant women during the second trimester, and to identify the factors influencing the level of pregnant women's GWG.

**Materials and Methods:** This was a randomized, controlled study comparing the number of pregnant women in the CAI and RCI groups who had a proper GWG during the four-week period.

**Results:** There were 70 and 80 participants in the CAI and RCI groups, respectively. The basic characteristics of the two groups at the beginning of the study were similar. The rate of the participants who had an appropriate GWG according to their pre-pregnancy BMI in both groups was comparable (p = 0.656, 0.307, 0.111, and 0.524 among the underweight, normal-weight, overweight and obese women, respectively). The number of participants who had an appropriate GWG was 50.0%, 47.8%, 23.1%, and 20.0% in the CAI group and 37.5%, 58.3%, 58.3%, and 50.0% in the RCI group. The GWG per week according to the participants' pre-pregnancy BMI was comparable in both groups (p = 0.585, 0.292, 0.087, and 0.614 in the underweight, normal-weight, overweight, and obese women, respectively). The multiparous women had a significantly increased possibility of having an appropriate GWG (p = 0.013).

**Conclusion:** Antenatal nutritional counseling using CAI was shown to be comparable to RCI in trying to achieve an appropriate GWG. The multiparous individuals had significant factors for having an appropriate GWG.

**Keywords:** weight gain, nutrition, counseling, computer-assisted instruction.

***Correspondence to:*** *Tharangrut Hanprasertpong, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot university, Ongkharak, Nakornnayok, Thailand. E-mail: tharangrut @hotmail.com; tharangrut@gmail.com*

**Received:** 31 May 2023, **Revised:** 7 January 2024, **Accepted:** 15 January 2024

# *ผลเปรียบเทียบการให้คำแนะนำเรื่องโภชนาการด้วยวิธีแตกต่างกันต่อการเพิ่มขึ้นอย่างเหมาะสมของน้ำหนักตัวหญิงตั้งครรภ์ระหว่างไตรมาสสอง: การศึกษาแบบสุ่มและมีกลุ่มควบคุมี*

***สุกัญญา เสรีรัตน์, กิตติพงษ์ คงสมบูรณ์, ธารารัตน์ หาญประเสริฐพงษ์***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อเปรียบเทียบการให้คำแนะนำเรื่องโภชนาการด้วยวิธีที่แตกต่างกัน 2 วิธี (การดูวีดิทัศน์กับแบบตัวต่อตัว) ต่อการเพิ่มขึ้นของน้ำหนักตัวอย่างเหมาะสมของหญิงตั้งครรภ์สุขภาพดี ระหว่างไตรมาสสอง และแสดงปัจจัยที่มีอิทธิพลต่อระดับการเพิ่มขึ้นของน้ำหนักตัวของหญิงตั้งครรภ์*

***วัสดุและวิธีการ:*** *เป็นการศึกษาแบบสุ่มและมีกลุ่มควบคุม เปรียบเทียบจำนวนหญิงตั้งครรภ์ที่มีการเพิ่มขึ้นของน้ำหนักตัวอย่างเหมาะสมในการติดตาม 4 สัปดาห์ ระหว่างกลุ่มที่ได้รับคำแนะนำเรื่องโภชนาการด้วยวิธีที่แตกต่างกัน 2 วิธี (การดูวีดิทัศน์กับแบบตัวต่อตัว)*

***ผลการศึกษา:*** *หญิงตั้งครรภ์ 70 และ 80 คน เข้าร่วมการศึกษา โดยเป็นกลุ่มที่ได้รับคำแนะนำเรื่องโภชนาการด้วยวิธีการดูวีดิทัศน์กับแบบตัวต่อตัว ตามลำดับ ข้อมูลพื้นฐานของหญิงตั้งครรภ์ทั้งสองกลุ่มเหมือนกัน อัตราส่วนของหญิงตั้งครรภ์มีการเพิ่มขึ้นของน้ำหนักตัวอย่างเหมาะสมตามดัชนีมวลกายก่อนการตั้งครรภ์ระหว่างสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่า p เท่ากับ 0.656, 0.307, 0.111, และ 0.524 ในกลุ่มน้ำหนักตัวน้อยเกินไป น้ำหนักตัวปกติ น้ำหนักเกิน และอ้วน ตามลำดับ) จำนวนหญิงตั้งครรภ์ที่มีการเพิ่มขึ้นของน้ำหนักตัวอย่างเหมาะสม เป็นร้อยละ 50.0, 47.8, 23.1 และ 20.0 ในกลุ่มได้รับคำแนะนำเรื่องโภชนาการด้วยวิธีการดูวีดิทัศน์ และเป็นร้อยละ 37.5, 58.3, 58.3 และ 50.0 สำหรับกลุ่มได้รับคำแนะนำเรื่องโภชนาการแบบตัวต่อตัว จำแนกตามดัชนีมวลกายเป็นกลุ่มน้ำหนักตัวน้อยเกินไป น้ำหนักตัวปกติ น้ำหนักเกิน และอ้วน ตามลำดับ น้ำหนักตัวหญิงตั้งครรภ์ที่เพิ่มขึ้นต่อสัปดาห์จำแนกตามระดับดัชนีมวลกายก่อนตั้งครรภ์ระหว่างสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่า p เท่ากับ 0.585, 0.292, 0.087 และ 0.614 ในกลุ่มน้ำหนักตัวน้อยเกินไป น้ำหนักตัวปกติ น้ำหนักเกิน และอ้วน ตามลำดับ) หญิงตั้งครรภ์หลายครั้งเพิ่มความเป็นไปได้ที่จะมีน้ำหนักเพิ่มระหว่างตั้งครรภ์เหมาะสม (ค่า p เท่ากับ 0.013).*

***สรุป:*** *การให้คำแนะนำเรื่องโภชนาการด้วยการดูวีดิทัศน์มีความเท่าเทียมกับการให้คำแนะนำแบบตัวต่อตัวที่จะทำให้หญิงตั้งครรภ์มีน้ำหนักเพิ่มระหว่างตั้งครรภ์เหมาะสม ปัจจัยที่มีแนวโน้มว่าน้ำหนักเพิ่มระหว่างตั้งครรภ์เหมาะสมคือ หญิงตั้งครรภ์หลายครั้ง*

***คำสำคัญ:*** *น้ำหนักเพิ่ม, โภชนาการ, การให้คำแนะนำ, ดูวีดิทัศน์*

## Introduction

Antenatal care (ANC) is an important medical service for pregnant women[1]. It mainly aims to promote and maintain the physical, social, and mental well-being of the pregnant woman and her fetus and to prepare for the postpartum period. Such care involves providing education about one's proper nutritional intake; adequate personal hygiene; the detection of medical, surgical, and obstetric complications; and preparing for the birth process and breastfeeding[2]. Meeting the nutritional requirements during pregnancy is crucial to proper fetal growth and development and to maintaining maternal health and preparing mothers to lactate sufficiently. Adverse pregnancy outcomes are more common in women who begin the gestation when they are undernourished or overweight/obese[3]. Maternal malnutrition increases the risk of fetal growth restriction, premature birth, fetal low-birth weight, and perinatal morbidity and mortality[3]. On the other hand, pregnant women who have a high body mass index (BMI) are at potential risk of several obstetric complications, including miscarriage, preeclampsia, gestational diabetes, obstructed labor, postpartum hemorrhage, obstetric-wound infection, and neonatal death[3, 4]. Moreover, preconception BMI and gestational weight gain (GWG) have been found to be important factors in maternal and fetal health[5]. In 2009, the American Institute of Medicine (IOM) recommended the GWG guidelines for better universal comprehension[6]. The recommended range of GWG per week during the second and third trimesters is classified according to pre-pregnancy BMI as follows: underweight (BMI < 18.5 kilograms (kg)/$m^2$) 1-1.3 pounds; normal weight (BMI 18.5-24.9 kg/$m^2$) 0.8-1 pounds; overweight (BMI 25-29.9 kg/$m^2$) 0.5-0.7 pounds; and obese (BMI ≥ 30 kg/$m^2$) 0.4-0.8 pounds[6].

Several interventions have been introduced to promote proper GWG, such as daily weighing, online intervention, and technology-based approaches[7-9]. Nutritional counseling and lifestyle modification are included in nearly all interventions. In our hospital, many counseling styles are offered to pregnant women, including routine, casual, individual methods (RCI), self-guided book reading, and group counseling with a unique computer-assisted pattern. Generally, nutritional counseling was constructed as an individual, casual style and did not separate from other topics. It was concluded with general care and genetic issues. The benefits to pregnant women have been questioned, especially when in-person counseling has been so difficult or even impossible during the pandemic. So, we initiated the individual computer-assisted instruction (CAI) as an alternative to the RCI. However, we had not, until this study, evaluated the effectiveness of both methods. We choose only the individual counseling method because of the importance of social distancing these days. We assumed that, if individual CAI is more effective or comparable to RCI, it is safer for healthcare providers. Thus, the main purpose of this study was to compare the individual CAI with the RCI as regards the proper weight gain according to the pre-pregnancy BMI of each participant. The second aim was to identify the factors influencing the level of pregnant women's weight gain.

## Materials and Methods

This prospective, randomized, controlled study was conducted among healthy pregnant women who were scheduled for antenatal visits during their second trimester at the Antenatal Outpatient Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Thailand, between May 2021 and February 2022. The exclusion criteria were multiple pregnancies, pregnant women who had a history of underlying disease, and/or who were previously diagnosed with diabetic mellitus. The study was approved by the institute's ethics

committee (SWUEC/E-471/2563) and was registered on the Thai Clinical Trials Registry (TCTR 20210225003). Informed consent from all the participants was obtained.

The participants were asked to complete a questionnaire which included their maternal age, education, parity, gravidity, occupation, religion, and family income. They were asked about the factors which may have influenced their weight gain, and this information was recorded. The data included their pre-pregnancy weight, height, pre-pregnancy BMI, a history of previous abnormal birth weight in a child, their family history of first- or second-degree diabetic mellitus, sleep duration for a day, working duration for a day, exercise regularity, number of main-course meals, dinner time, duration from dinner to sleep (hours), and any history of gastrointestinal disturbance (constipation, hemorrhoids, heartburn). The visual analogue scales (VAS) were examined to demonstrate the level of the participants' perceptions regarding abnormal weight gain dangerous and necessary for weight gain, and diet-intake control. Then, the participants were randomly allocated to receive counseling by the individual CAI or RCI method. Previously numbered, sealed, opaque envelopes were used in this process. The given information in the CAI was created by a second-year resident (the first author listed in this study) in the Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, under the Royal Thai College of Obstetricians and Gynecologists' curriculum, with supervision by the Maternal Fetal Medicine staff (the third author) at the Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University.

Crucial information pertaining to pregnant women was included, such as the importance of proper GWG, maternal and neonatal complications related to inappropriate GWG, healthy food, and lifestyle-modification material. After the antenatal clinic was finished and an appointment was scheduled, the participants in the RCI group were counseled about nutrition as routine, causal antenatal visits. The RCI took approximately 15 minutes including nutritional education and other routine antenatal care. The main content about nutrition was advised for the attending physician were similar to the content in CAI script but did not have a definite script. The participants in the CAI groups were given one round of the CAI script. The CAI took approximately 20 minutes. Participants in both groups were given an opportunity to ask any questions after finishing the counseling. The service doctors were not advised of additional information, except to answer the participants' questions.

Following the CAI or RCI, all the participants were discharged from the antenatal clinic, and their next appointment was made for four weeks later. At that time, all participants were weighed and recorded. A digital weigh scale (Seca, with a decimal point or 0.1 kg and a maximum of 200 kg/ 440 pounds) was used for each person. Their frequency of exercise was classified as either regular or irregular. Regular exercise was defined as aerobic work-out on three or more days per week, with each session lasting at least 15 minutes. Less than that was defined as irregular exercise. Their frequency of unhealthy food intake was classified into high and low frequency. High was defined as eating two or more types of unhealthy food at least twice a week. Unhealthy foods included highly processed ones such as fast food, snack food, low-in-nutrients items, and high in flours, sodium, and sugar, such as chips, cookies, cakes and sweet cereals.

The required sample size was estimated by using a formula for a randomized, controlled trial for binary data with continuity correction. In a previous study, 45.7% of pregnant women had proper weight gain after receiving individual, in-person, or e-mail counseling. There was no study

focusing on the CAI. We expected about 55% of the pregnant women to properly gain weight after the CAI. To achieve an alpha of 0.05, the sample size required for each group was around 68 subjects or 136 in total. Allowing for 20% lost or missing data, 164 participants were required.

The demographic and clinical characteristics of the patients at baseline within each group were examined by tabulating percentages or means and standard deviation or the median and interquartile range (IQR), depending on the distribution. The number of participants who had proper and improper GWG in the CAI and RCI groups was compared according to their pre-pregnancy BMI, using the Pearson chi-square test. The GWG per week between the CAI and RCI groups were compared according to their BMI by using the independent t-test or the Mann-Whitney U test, depending on the distribution. Lastly, the possible factors associated with proper GWG were identified using co-linearity and binary, logistic regression. In all statistical tests, p values of $< 0.05$ were considered significant.

## Results

One hundred and sixty-four pregnant women were enrolled and randomized into 82 participants for each group. 12 and 2 participants in CAI and RCI groups, respectively, lost to follow-up. Thus, 70 and 80 participants were in the CAI and RCI groups, respectively, for analysis. The flow of participants and lost numbers are summarized in Fig. 1. At the beginning, the participants' demographic and clinical data in both groups were similar (Table 1).

The rate of participants in the groups who had an appropriate GWG was compared according to their pre-pregnancy BMI, as shown in Table 2. It was comparable between the groups. The comparison of the GWG per week in both groups according to their pre-pregnancy BMI is shown in Table 3. It was comparable in both groups. Table 4 presents the logistic regression analysis for factors that may have influenced the possibility of having an appropriate GWG. Only multiparous participants had a significantly increased possibility of having an appropriate GWG.

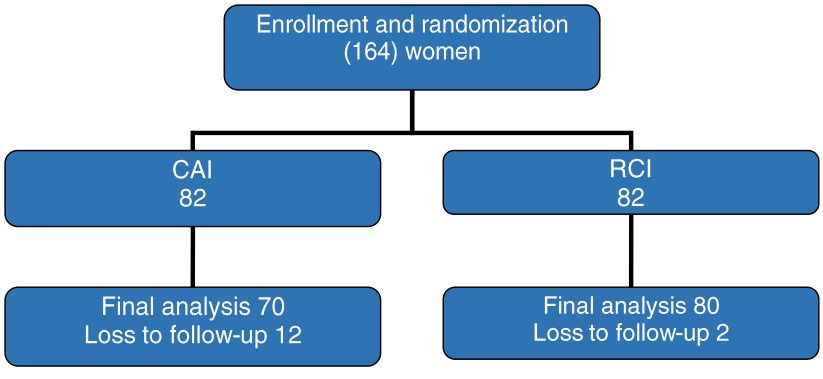


Fig. 1. Flow diagram showing the overall outcomes of all screening cases.

**Table 1.** Baseline characteristics (n = 150).

| Characteristics | RCI (n = 80) | CAI (n = 70) | p value |
|---|---|---|---|
| Age (years), mean (SD) | 28.19±5.087 | 27.64±4.923 | 0.508* |
| Level of education, n (%) | | | 0.174** |
| Less than primary school | 12 (15.0) | 16 (22.9) | |
| Primary school-bachelor's | 65 (81.3) | 48 (68.6) | |
| Higher than bachelor's | 3 (3.8) | 6 (8.6) | |
| Primigravida, n (%) | | | 0.894** |
| Yes (G = 1) | 34 (42.5) | 29 (41.4) | |
| No (G ≥ 2) | 46 (57.5) | 41 (58.6) | |
| Occupation, n (%) | | | 0.333** |
| Employee | 21 (26.3) | 23 (32.9) | |
| Housewife | 21 (26.3) | 16 (22.9) | |
| Government officer | 8 (10.0) | 13 (18.6) | |
| Agriculture | 2 (2.5) | 2 (2.9) | |
| Others | 28 (35.0) | 16 (22.9) | |
| Religion, n (%) | | | 0.289** |
| Buddhist | 64 (80.0) | 62 (88.6) | |
| Muslim | 15 (18.8) | 7 (10.0) | |
| Others | 1 (1.3) | 1 (1.4) | |
| History of abortion, n (%) | | | 0.543** |
| Yes | 14 (17.5) | 15 (21.4) | |
| No | 66 (82.5) | 55 (78.6) | |
| Family income (Bath) | | | 0.186** |
| < 15,000 | 21 (26.3) | 18 (25.7) | |
| 15,000 – 29,999 | 33 (41.3) | 34 (48.6) | |
| 30,000 – 50,000 | 21 (26.3) | 18 (25.7) | |
| > 50,000 | 5 (6.3) | 0 (0) | |
| Gestational age (weeks), n (%) | | | 0.301** |
| 14-22 | 52 (65.0) | 51 (72.9) | |
| 23-28 | 28 (35.0) | 19 (27.1) | |
| Height (cm), mean (SD) | 159.43±5.852 | 158.44±5.946 | 0.310* |
| Pre-pregnancy weight (kg), median (IQR) | 56 (48.5-64.0) | 54 (50.0-62.0) | 0.946*** |
| Pre-pregnancy BMI, median (IQR) | 22.15 (19.35-24.85) | 22.00 (19.5-25.4) | 0.670*** |
| Pre-pregnancy BMI | | | 0.245** |
| Underweight | 16 (20.0) | 6 (8.6) | |
| Normal | 48 (60.0) | 46 (65.7) | |
| Overweight | 12 (15.0) | 13 (18.6) | |
| Obesity | 4 (5.0) | 5 (7.1) | |
| Previous child's abnormal weight, n (%) | | | |
| Yes | 4 (5.0) | 2 (2.9) | |
| No | 76 (95.0) | 68 (97.1) | |
| Family history of DM, n (%) | | | 0.805** |
| Yes | 22 (27.5) | 18 (25.7) | |
| No | 58 (72.5) | 52 (74.3) | |
| Sleep duration (hours), median (IQR) | 8 (8-9) | 8 (8-8) | 0.412*** |
| Work duration (hours), median (IQR) | 8 (0.5-8) | 7 (0-8) | 0.689*** |
| Exercise frequency n, (%) | | | 0.734** |
| Regular | 11 (13.8) | 11 (15.7) | |
| Irregular | 69 (86.3) | 59 (84.3) | |
| Number of main-course meals per day, n (%) | | | 0.678** |
| ≤ 2 | 13 (16.3) | 14 (20.0) | |
| 3-4 | 64 (80.0) | 55 (78.6) | |
| > 4 | 3 (3.8) | 1 (1.4) | |
| Dinner-to-sleep duration (hours), n (%) | | | 0.361** |
| < 3 | 25 (31.3) | 24 (34.3) | |
| 3-5 | 45 (56.3) | 42 (60.0) | |
| > 5 | 10 (12.5) | 4 (5.7) | |
| Smoking or alcohol, n (%) | | | 0.685** |
| Yes | 4 (5.0) | 2 (2.9) | |
| No | 76 (95.0) | 68 (97.1) | |
| GI discomfort, n (%) | | | |
| presence | 25 (31.3) | 32 (45.7) | |
| absence | 55 (68.8) | 38 (54.3) | |
| Attitude about abnormal weight (VAS), median (IQR) | 5 (3.15-6.15) | 4.25 (2.9-5.2) | 0.116*** |
| Attitude about controlling weight (VAS), median (IQR) | 10 (8.35-10.0) | 10 (8.1-10.0) | 0.854*** |
| Frequency of unhealthy food intake ** | | | 0.304** |
| high | 41 (51.3) | 30 (42.9) | |
| Low | 39 (48.8) | 40 (57.1) | |

* Independent t-test, ** Pearson chi-square test, *** Mann-Whitney U test

RCI: routine, casual, individual, CAI: computer-assisted instruction,

SD: standard deviation, IQR: interquartile range, BMI: body mass index, DM: diabetes mellitus, VAS: visual analogue scales.

**Table 2.** Comparisons of the number of participants who had an appropriate GWG involving the CAI and RCI groups according to their pre-pregnancy BMI.

| Groups | Weight gain | | RR | 95%CI | p value |
|---|---|---|---|---|---|
| | appropriate | inappropriate | | | |
| Underweight | | | | | |
| CAI, n (%) | 3 (50.0) | 3 (50.0) | 1.333 | 0.481-3.698 | 0.655** |
| RCI, n (%) | 6 (37.5) | 10 (62.5) | | | |
| Normal weight | | | | | |
| CAI, n (%) | 22 (47.8) | 24 (52.2) | 0.820 | 0.558–1.205 | 0.307** |
| RCI, n (%) | 28 (58.3) | 20 (41.7) | | | |
| Overweight | | | | | |
| CAI, n (%) | 3 (23.1) | 10 (76.9) | 0.396 | 0.131-1.190 | 0.111** |
| RCI, n (%) | 7 (58.3) | 5 (41.7) | | | |
| Obesity | | | | | |
| CAI, n (%) | 1 (20.0) | 4 (80.0) | 0.400 | 0.054-2.980 | 0.524** |
| RCI, n (%) | 2 (50.0) | 2 (50.0) | | | |

** Pearson chi-square test

GWG: gestational weight gain, CAI: computer-assisted instruction, RCI: routine, casual, individual, BMI: body mass index, RR: risk ratio, CI: confidence interval.

**Table 3.** Comparisons of GWG per week (kg/wk.) among participants in both the RCI and CAI groups according to their pre-pregnancy BMI.

| Gestational weight gain per week (Kg/wk) | CAI | RCI | p value |
|---|---|---|---|
| Underweight, mean (SD) | 0.52 ± 0.22 | 0.48 ± 0.24 | 0.585* |
| Normal weight, median (IQR) | 0.46 (0.40-0.73) | 0.47 (0.38-0.55) | 0.292** |
| Overweight, median (IQR) | 0.52 (0.37-0.70) | 0.31 (0.25-0.55) | 0.087** |
| Obesity, mean (SD) | 0.37 ± 0.13 | 0.45 ± 0.31 | 0.614* |

* Independent t-test, **Mann-Whitney U test

GWG: gestational weight gain, RCI: routine, casual, individual, CAI: computer-assisted instruction, BMI: body mass index, RR: risk ratio, SD: standard deviation, IQR: interquartile range.

**Table 4.** Factors associated with appropriate weight gain (n = 150).

| Factors | Crude OR | 95%CI | p value | Adjusted OR | 95%CI | p value |
|---|---|---|---|---|---|---|
| Parity | | | | | | |
| Multiparity | 2.243 | 1.153-4.362 | 0.017 | 2.384 | 1.198-4.742 | 0.013 |
| Nulliparous | 1 | - | - | 1 | - | - |
| Pre-pregnancy BMI | | | | | | |
| Normal weight | 1.756 | 0.897-3.439 | 0.101 | 1.911 | 0.947-3.856 | 0.071 |
| Abnormal weight | 1 | - | - | 1 | - | - |
| Group | | | | | | |
| RCI | 1.643 | 0.860-3.140 | 0.133 | 1.678 | 0.850-3.312 | 0.136 |
| CAI | 1 | - | - | 1 | - | - |
| Religion | | | | | | |
| Muslim and others | 2.018 | 0.822-4.951 | 0.125 | 2.120 | 0.820-5.480 | 0.121 |
| Buddhist | 1 | - | - | 1 | - | - |

Adjusted with gravida, pre-pregnancy BMI, group and religion

OR: odds ratio, CI: confidence interval, BMI: body mass index, RCI: routine, casual, individual, CAI: computer-assisted instruction.

## Discussion

A healthy lifestyle is crucial for pregnant women. The old- fashioned belief is that pregnant women must "eat for two" and that eating more is better for their fetus. Previous study found that 20-40% of pregnant women in Europe excessively gained weight, beyond the recommended GWG[10]. Such excessive weight increased the prevalence of chronic diseases and healthcare costs involved in additional obstetric complications[11]. Healthcare providers should participate in routine antenatal counseling to convince patients that eating more is in fact not advisable at all. The current study is the first to compare the RCI and CAI used for antenatal nutritional counseling in Thailand during the COVID-19 pandemic. RCI is a two-way, face-to-face form of communication. It is easier for physicians to observe the patients' participation and communication than when using the CAI. However, CAI is safer at this time, due to the need for social distancing. The results of comparison of the number of participants who had an appropriate GWG were comparable to those in the RCI groups, according to their pre-pregnancy BMI. Thus, it is reasonable to apply it in clinical practice to avoid close contact between healthcare providers and pregnant women. However, the benefits of both counseling methods in reducing adverse pregnancy outcomes could not be concluded from our study because we did not follow the participants until they gave birth. Thus, further study is planned, and the pregnancy outcomes should be followed until delivery. An important limitation of our study was that it was no blinded for service doctors who gave the RCI. So, we are concerned that the biases of such doctors may have interfered with our results. However, only one round of CAI script attention may not be enough. Opportunities for repeated attendance are our suggestion. Regarding CAI counseling, there has so far been no CAI on antenatal nutritional counseling in Thailand. There were two studies of pregnant Thai women during their antepartum and postpartum period. To enhance our knowledge of pregnant women before they undergo their second-trimester genetic amniocentesis, the CAI was less effectiveness than reading brochures by themselves[12]. As for improving the LATCH scores among breastfeeding women, the CAI was not shown to be significantly better than routine postpartum care[13].

Attention to the GWG per week, although it was comparable between both groups, it tended to have an improper range regarding the overweight and obese pregnant women, as contrasted to those who were underweight or had a normal weight. It was similar to the findings of previous studies which focused on the GWG in overweight and obese pregnant women[14,15]. We postulated that the behavioral style and individual metabolism of overweight and obese pregnant women may be linked to a risk for excessive GWG. Several previous studies have intensively focused on this pregnancy group[14-16]. However, our study failed to identify any significant effects of BMI on GWG. Parity was the only variable which indicated a significant effect on the appropriate GWG. Multiparous women can achieve the appropriate GWG more than nulliparous women can. This finding was different from that in the previous study which investigated how to minimize obese women's total weight gain during pregnancy to less than 7 kg[16]. It reported that the percentage of nulliparous obese women who successfully gained less than 7 kg was greater than the number in the unsuccessful group. They postulated that nulliparous women might be more expected for their first children and thus give higher priority to a lifestyle than do multiparous women. The different results may be explained by the different study objectives and participants' characters. We included all participants' BMI, and this may have influenced the outcome. Greater success in achieving the appropriate GWG among multiparous pregnant women may be caused by their experience with

previous adverse pregnancy outcomes and/or delivery difficulties, along with their awareness of difficulties with postpartum weigh reduction. These factors may likely have inspired the multiparous women to better control their weight.

## Conclusion

In conclusion, it is clear that, during this COVID epidemic when social distancing is essential, CAI counseling is comparable to RCI for appropriate weight management among antenatal women. Universal distribution is our suggestion.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References


1. Rooney CIE, the WHO Maternal Health and Safe Motherhood Program. Antematal care and maternal health: How effective is it? A review of the evidence" [update 1992; cite 2022 May 12]. Available from: http://apps.who.int>iris>bitstream.
2. Ekabua J, Ekabua K, Njoku C. Proposed framework for making focused antenatal care service accessible: A review of the Nigerian setting. ISRN Obstet Gynecol 2011;2011:253964.
3. Plecas D, Plesinac S, Vucinic O. Nutrition in pregnancy: Basic principles and recommendations. Srp Arh Celok Lek 2014;142:125-30.
4. Holton S, East C, Fisher J. Weight management during pregnancy: A qualitative study of women's and care providers' experiences and perspectives. BMC Pregnancy Childbirth 2017;17:351.
5. Kiani Asiabar A, Amin Shokravi F, Hajifaraji M, Zayeri F. The effects of an educational intervention in early pregnancy with spouses' participation in optimal gestational weight gain in pregnancy: A randomized controlled trial. Health Educ Res 2018;33:535-47.
6. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight gain during pregnancy: Reexamining the guidelines. Rasmussen KM, Yaktine AL, editors. Washington (DC): National Academies Press (US); 2009.
7. Chao AM, Srinivas SK, Studt SK, Diewald LK, Sarwer DB, Allison KC. A pilot randomized, controlled trial of a technology-based approach for preventing excess weight gain during pregnancy among women with overweight. Front Nutr 2017;5:57.
8. Olson CM, Groth SW, Graham ML, Reschke JE, Strawderman MS, Femandez ID. The effectiveness of an online intervention in preventing excessive gestational weight gain: the e-moms roc randomized controlled trial. BMC Pregnancy Childbirth 2018;18:148.
9. Arthur C, Di Corleto E, Ballard E, Kothari A. A randomized, controlled trial of daily weighing in pregnancy to control gestational weight gain. BMC Pregnancy Childbirth 2020;20:223.
10. Hajian S, Aslani A, Sarbakhsh P, Fathnezhad-Kazemi A. The effectiveness of healthy lifestyle interventions on weight gain in overweight pregnant women: A cluster-randomized, controlled trial. Nursing Open 2020;7:1876-86.
11. Mourtakos SP, Tambalis KD, Panagiotakos DB, Antonogeorgos G, Arnaoutis G, Karteroliotis K, et al. Maternal lifestyle characteristics during pregnancy and the risk of obesity in the offspring: A study of 5125 children. BMC Pregnancy Childbirth 2015;66:1-8.
12. Hanprasertpong T, Rattanaprueksachart R, Janwadee S, Geater A, Kor-anantakul O, Suwanrath C, et al. Comparison of the effectiveness of different counseling methods before second-trimester genetic amniocentesis in Thailand. Prenat Diagn 2013;33: 1189-93.
13. Sroiwatana S, Puapornpong P. Outcomes of video-assisted teaching for latching in postpartum women: A randomized, controlled trial. Breastfeed Med 2018;13: 366-70.
14. Pawalia A, Kulandaivelan S, Savant S, Yadav VS. Effect of behavioral interventions for obesity prevention in pregnancy on the adequacy of gestational weight gain and retention: The metabolic health of Indian women. Ser J Exp Clin Res 2020;21:35-42.
15. Olander EK, Hill B, Skouteris H. Healthcare professionals' training regarding gestational weight gain: Recommendations and future directions. Curr Obes Rep 2021;10:116-24.
16. Claesson IM, Sydsjo G, Brynhildsen J, Cedergren M, Jeppsson A, Nystrom F, et al. Weight-gain restriction for obese pregnant women: A case-control intervention study. BJOG 2008;115:44-50.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 287-294.

## GYNAECOLOGY

# Comparison of the Efficacy between Conjugated Equine Estrogen versus Nonsteroidal Anti-inflammatory Drug for the Cessation of Uterine Bleeding among Contraceptive Implant Users: A randomized controlled trial

Salinee Polyota, M.D.*,
Reuthairat Tungmunsakulchai, M.D.*,
Thumwadee Tangsiriwatthana, M.D.*

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

## ABSTRACT

**Objectives:** To evaluate the effect of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs on the controlling of abnormal uterine bleeding in hormonal subdermal implant users.

**Materials and Methods:** Between July 2022 and April 2023, participants with etonogestrel subdermal implants who complained of abnormal uterine bleeding were randomly allocated into two groups. The study group (n = 32) received 0.625 mg of conjugated equine estrogen orally twice a daily for five days, while the control group (n = 32) received 500 mg of mefenamic acid orally three times a daily for five days. The duration of bleeding cessation was evaluated.

**Results:** Baseline characteristics including age, BMI, duration of implant use, endometrial thickness, and pattern of bleeding were not statistically different in both groups. The duration of bleeding cessation was significantly shorter in the conjugated equine estrogen group (5.9 ± 3.4 vs 7.9 ± 3.9 days, mean difference 2.0 days (95%CI 0.01 to 0.02, $p < 0.05$)).

**Conclusion:** Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding in etonogestrel subdermal implant use.

**Keywords:** abnormal uterine bleeding, hormonal subdermal implant, conjugated equine estrogen, mefenamic acid.

***Correspondence to:*** *Salinee Polyota, M.D., Department of Obstetrics and Gynecology, KhonKaen Hospital, KhonKaen 40000, Thailand. E-mail: S.polyota@gmail.com*

**Received:** 27 September 2023, **Revised:** 17 January 2024, **Accepted:** 19 January 2024

# *เปรียบเทียบประสิทธิภาพการใช้ยาคอนจูเกตเอสโตรเจนและยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ในการรักษาภาวะเลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังการศึกษาแบบสุ่ม*

***สาลินี พลโยธา, ฤทัยรัตน์ ตั้งมั่นสกุลชัย, ทุมวดี ตั้งศิริวัฒนา***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อศึกษาเปรียบเทียบผลของการใช้ยาตอนจูเกตเอสโตรเจนและยาต้านการอักเสบที่ไม่ใช่เสตียรอยด์ในการควบคุมเลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝั่งใต้ผิวหนัง*

***วัสดุและวิธีการ:*** *สตรีที่ได้รับการวินิจฉัยเบื้องต้นว่ามีภาวะเลือดออกผิดปกติทางช่องคลอดหลังจากการใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรลช่วงเวลาระหว่างเดือนกรกฎาคม พ.ศ. 2565 ถึง เมษายน พ.ศ. 2566 ได้รับการสุ่มแบ่งเป็นสองกลุ่มกลุ่มศึกษาได้รับยาคอนจูเกตเอสโตรเจน (0.625 มก./แคปซูล) รับประทานครั้งละ 1 แคปซูลวันละ 2 ครั้ง หลังอาหารเช้า-เย็น เป็นระยะเวลา 5 วัน จำนวน 32 คน และกลุ่มควบคุมได้รับยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ (250 มก./ แคปซูล) รับประทาน ครั้งละ 2 แคปซูล วันละ 3 ครั้ง หลังอาหารเช้า-เที่ยง-เย็น เป็นระยะเวลา 5 วัน จำนวน 32 คน ทำการประเมินจำนวนวันที่เลือดออกจนหยุดหลังได้รับการรักษา*

***ผลการศึกษา:*** *จำนวนวันที่เลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรลจนหยุดหลังได้รับการรักษาด้วยยาคอนจูเกตเอสโตรเจนน้อยกว่าการรักษาด้วยยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์อย่างมีนัยสำคัญทางสถิติ 5.9 ± 3.4 วัน และ 7.9 ± 3.9 วัน ตามลำดับ โดยค่าเฉลี่ยแตกต่างกัน 2.0 วัน (95%CI 0.01 ถึง 0.02, $p < 0.05$)*

***สรุป:*** *กลุ่มยาคอนจูเกตเอสโตรเจนมีประสิทธิภาพในการลดจำนวนวันที่เลือดออกผิดปกติทางช่องคลอดในสตรีที่ใช้ฮอร์โมนฝังใต้ผิวหนังชนิดอีโทโนเจสเตรล*

***คำสำคัญ:*** *เลือดออกผิดปกติทางช่องคลอด,ฮอร์โมนฝังใต้ผิวหนัง, ยาคอนจูเกตเอสโตรเจน, ยาเมเฟนามิค แอซิด*

## Introduction

The hormonal subdermal implant is the first long-acting progestin contraceptive method, The Population Council's registered trademark for one capsule implant releasing Etonogestrel[1]. The implant is efficacious and convenient and presents fewer user compliance problems[2]. However, abnormal uterine bleeding is the most common reason for discontinuing its use[1,2]. Abnormal uterine bleeding is common in the first month of use but diminishes with continued use[2]. Mechanism of abnormal uterine bleeding in subdermal implant users were abnormal endometrial vessels and abnormal endometrial environment[2]. Although these side effects are not dangerous, they can be upsetting, necessitating counseling and support to overcome discontinuation[3].

There are several treatment options available for women who have abnormal uterine bleeding while using hormonal subdermal implants, including conjugated equine estrogen, ethinyl estradiol, combined hormonal contraceptives, and nonsteroidal anti-inflammatory drugs such as mefenamic acid, ibuprofen, and tranexamic acid[4-7].

Conjugated equine estrogen and nonsteroidal anti-inflammatory drugs have been used to reduce bleeding[8]. Previous studies have shown that conjugated equine estrogen is significantly reduces irregular bleeding in hormonal subdermal implant users[8].

A recent study compared the efficacy of mefenamic acid and placebo, and they found that mefenamic acid was more effective in short-term control of irregular bleeding and spotting within 7 days after initiation of treatment (76% vs 27%, respectively), and the mean number of days of bleeding and spotting after initiation of mefenamic acid treatment (11.6 vs 17.2 days, respectively). The effectiveness of mefenamic acid treatment, reinforcing the hypothesis that the mechanism of this disorder involves altered prostaglandin production[9,10]. In another study comparing the efficacy of, combined oral contraceptive pills vs mefenamic acid, 76.0% vs 35.7% of women who received combined oral contraceptive pills stopped bleeding within seven days after the initiation treatment[11]. Moreover, the mean duration of bleeding and spotting days in combined oral contraceptive pills was significantly shorter than mefenamic acid group (7.29 ± 3.16 vs 10.57 ± 4.14 days)[11].

The most common adverse effect of combined oral contraceptive pills is breakthrough bleeding, but women who use combined oral contraceptive pills will also complain of nausea, headaches, abdominal cramping, breast tenderness, and an increase in vaginal discharge or decreased libido. So, most of these women being intolerant to the side effects of combined oral contraceptive pills and long duration of use usually stop using it while under the protocol[11,12]. Alternatively, conjugated equine estrogen induces endometrial epithelial proliferation and may thus effectively terminate prolonged bleeding episodes in progestogen users with short course therapy and fewer side effects than combined hormonal contraceptives[4-6, 8]. Thus far, no study has demonstrated that conjugated equine estrogen significantly reduces irregular bleeding in users of hormonal subdermal implants.

No study has compared the efficacy of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs in the treating of bleeding irregularities in hormonal subdermal implant users. In the current study, we evaluated the effectiveness of conjugated equine estrogen and nonsteroidal anti-inflammatory drugs in the control of abnormal uterine bleeding in hormonal subdermal implant users.

## Materials and Methods

This single-blind, randomized controlled trial study was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital. It was approved by the Khon Kaen Hospital Institute Review Board in Human Research (reference number: KEF65014).

Eligible participants included non-pregnant

women aged ≥ 15 years used single rod of 68 mg etonogestrel insertion for 3 to 36 months for the first time, complained of abnormal uterine bleeding for the first time and to exhibit none of exclusion criteria were applied: 1) gynecological or medical diseases was cause uterine bleeding, 2) contraindication or allergy to estrogen or nonsteroidal anti-inflammatory drugs, 3) chronic use of nonsteroidal anti-inflammatory drugs before the enrollment.

Participants were informed of the study at the family planning clinic. Written informed consent was obtained from each participant before enrollment. Participants were randomly allocated by computer generation using a block of four into two groups, the conjugated equine estrogen group (study group) and the mefenamic acid group (control group). Allocation concealment was achieved using sealed opaque envelopes.

Baseline characteristics were recorded, including age, body mass index (BMI), baseline characteristics of abnormal uterine bleeding (spotting, hypermenorrhea, and menorrhagia), and endometrial thickness. The participants were informed about the outcomes and were asked to record any episode of "abnormal uterine bleeding" (spotting, hypermenorrhea, and menorrhagia) after using etonogestrel subdermal implants. Spotting was defined as unexpected bleeding with no required tampons or sanitary napkins. Hypermenorrhea was defined as heavy bleeding over 80 ml, menorrhagia was defined as bleeding longer than 7 days, and "no bleeding" was defined as the duration of bleeding cessation after treatment[13,14]. After enrollment, a gynecological examination, urine pregnancy test, and transabdominal ultrasound were performed to rule out any other possible confounding causes of bleeding or spotting and measurement of endometrial thickening.

Sixty-four subjects were recruited: the study group (n = 32) received 0.625 mg of conjugated equine estrogen orally twice daily for five days, and the control group (n = 32) received 500 mg of mefenamic acid orally three times daily for five days. The pharmacist prepared all the drugs and kept them in a sealed opaque package. The assignment of both groups was blinded. The treatment was not identified in the case record form until code numbers were broken at the end of the study.

All participants were appointed at the end of week 1 after their initial treatment at the clinic or by phone. During the follow-up period, the participants were told of the bleeding cessation, the total number of bleeding or spotting days, and any other adverse effects to the investigator. If the bleeding did not stop, two additional capsules of tranexamic acid (500 mg/capsule) were administered orally twice daily for 5 days.

The sample size was calculated based on a pilot study of 30 participants with a power of 90%, $\alpha$ level of 0.05, and a dropout rate of 10%. A total of 64 participants (32 in each group) was required. Data were analyzed based on an intention-to-treat analysis using STATA version 14. The Student's t-test and Chi-squared or Fisher's exact test were used to analyze continuous and categorical data, as appropriate. A p-value < 0.05 was considered statistically significant.

## Results

Between June 2022 and April 2023, 64 eligible women who visited the family planning clinic at Khon Kaen Hospital were enrolled in the study and randomly assigned into two groups (32 in the study group and 32 in the control group). No dropouts occurred (Fig. 1). Baseline characteristics were similar between the groups, including age, body mass index (BMI), baseline characteristics of abnormal uterine bleeding, and endometrial thickness (Table 1).

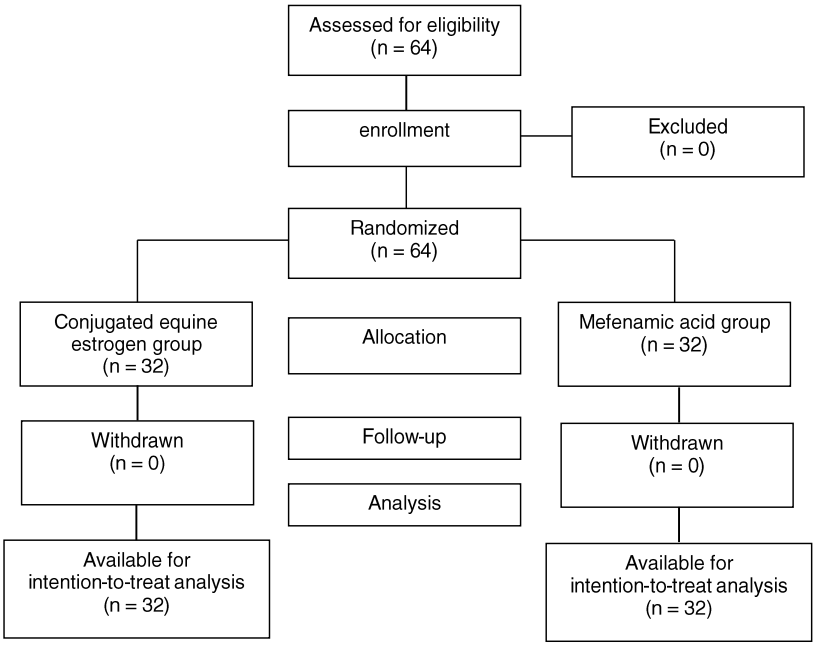


**Fig. 1.** Study flow.

**Table 1.** Demographics and Clinical characteristics of participants.

| | **Conjugated equine estrogen (n = 32)** | **Mefenamic acid (n = 32)** | **p value** |
|---|---|---|---|
| Age (years) | 19.5 ± 4.1 | 18.9 ± 3.6 | 0.52[t] |
| BMI (kg/m$^2$) | 21.6 ± 4.1 | 20.2 ± 4.6 | 0.19[t] |
| Duration of implant use (months) | 7.5 ± 5.9 | 5.3 ± 4.0 | 0.19[t] |
| Endometrial thickness (mm.) | 4.0 ± 2.4 | 3.7 ± 2.5 | 0.36[c] |
| Pattern of bleeding, n (%) | | | 0.69[f] |
| - Spotting | 18 (56.3) | 19 (59.4) | |
| - Menorrhagia | 4 (12.4) | 2 (6.2) | |
| - Hypermenorrhea | 10 (31.3) | 11 (34.4) | |

Data were presented as number (%), mean ± standard deviation.
P value corresponded to [t] Student t-test, [c] Chi-square test or [f] Fisher's exact test.

The duration of bleeding cessation after initial treatment was significantly shorter in the conjugated equine estrogen group, about 5.9 days, than in the mefenamic acid group, about 7.9 days (5.9 ± 3.4 days vs 7.9 ± 3.9 days). The mean difference was 2.0 days (95% CI 0.01 to 0.02, p = 0.01). Bleeding patterns after

contraceptive implants were categorized as follows: the spotting subgroup in the conjugated equine estrogen group (56.3%) and the mefenamic acid group (59.4%); the hypermenorrhea subgroup in the conjugated equine estrogen group (31.3%) and the mefenamic acid group (34.4%); the menorrhagia subgroup in the conjugated equine estrogen group (12.4%); and the mefenamic acid group (6.2%). For the premarin group, persistent bleeding after treatment within 7 days is the spotting subgroup (27.8%), the hypermenorrhea subgroup (10%), and there are no cases in the menorrhagia subgroup. Therefore, in the mefenamic acid group, persistent bleeding after treatment within 7 days is the spotting subgroup (36.8%), the hypermenorrhea subgroup (18.2%), and there were no cases in the menorrhagia subgroup (Table 2).

**Table 2.** Result.

| | Conjugated equine estrogen (n = 32) | Mefenamic acid (n = 32) | Mean difference (95% confidence interval) | p value |
|---|---|---|---|---|
| Duration of bleeding cessation (day)* | 5.9 ± 3.4 | 7.9 ± 3.9 | 2.0 (0.01-0.02) | 0.01[t] |
| ≤ 7 Days to bleeding cessation n (%) | 26 (81.3) | 23 (71.9) | - | 0.38[c] |
| Adverse events, n (%) | 1 (3.1) | 3 (9.4) | - | 0.61[f] |
| - Stomach upset or cramps | | | | 0.36 [c] |
| Duration of medication adherence (day) | 4.6 ± 0.8 | 4.9 ± 0.34 | 0.3 (0.51-0.35) | 0.43[t] |
| Reason for non-adherences | 3 (9.4) | 2 (6.3) | - | 1.00[f] |
| - Get better from bleeding | | | | |

Data were presented as number (%), mean ± standard deviation
P value corresponded to [t] Student t-test, [c] Chi-square test, [f] Fisher's exact test.
* Significant at p value < 0.05

The percentage of bleeding cessation within 7 days after initiation of treatment was higher in conjugated equine estrogen than in the mefenamic acid group (81.3% vs 71.9%) (Table 2).

Four participants experienced mild symptoms of stomach upset in the present study: one in the conjugated equine estrogen group and three in the mefenamic acid group. Notwithstanding, symptoms Nausea/vomiting, Headache, Breast tenderness or swelling were not severe enough to discontinue the treatment (Table 2).

The mean duration of adherence was not significantly different between the conjugated equine estrogen, about 4.5 days and mefenamic acid groups, about 4.9 days (4.5 ± 0.8 days vs 4.9 ± 0.3 days, p = 0.428). The reason for non-adherence was that participants were feeling well enough to skip doses: 3 in the study group and 2 in the control group (Table 2).

In the satisfaction study with both medication groups, it was found that in the Premarin group, there was a high satisfaction rate of 75%. Additionally, in the mefenamic acid group, a satisfaction rate of 66.7% was observed.

## Discussion

The results of the current trial showed that the duration of bleeding cessation after the initial treatment was significantly shorter in the study (conjugated equine estrogen) group than in the control (mefenamic acid) group (5.9 ± 3.4 days vs 7.9 ± 3.9 days, mean difference 2.0 days (95%CI 0.01 to 0.02, p < 0.05).

Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding associated with hormonal subdermal implant use, which demonstrates that conjugated equine estrogen is effective in reducing irregular bleeding among hormonal subdermal implant users. The most common bleeding pattern after contraceptive implants was spotting (57.8%), hypermenorrhea (32.8%), and menorrhagia (9.4%). The percentage of women who stopped bleeding within 7 days after initiation of treatment was higher after conjugated equine estrogen treatment than after mefenamic acid treatment (81.3% vs 71.9%, p = 0.38), albeit the difference was not statistically significant. The percentage of bleeding cessation within 7 days after mefenamic acid treatment is like those of a previously published study (76.0%)[7]. The patient group with a high incidence of persistent bleeding after treatment within 7 days is the spotting subgroup in the premarin group (27.8%), and the mefenamic acid group (36.8%). When subgroup bleeding patterns were analyzed, it was observed that conjugated equine estrogen had a lower percentage of persistent bleeding compared to mefenamic acid in all subgroups. Conjugated equine estrogen induces endometrial epithelial proliferation and may effectively terminate prolonged bleeding episodes in progestogen users. Exogenous estrogens (i.e., conjugated equine estrogen, either alone or in combination with levonorgestrel) have successfully been used to treat irregular or prolonged bleeding during contraceptive implants[4,6]. Furthermore, conjugated equine estrogen has low side effects and mild symptoms of stomach upset, which is not a common reason for discontinued use.

However, effectively managing uterine bleeding in etonogestrel subdermal implant users hinges on the importance of providing comprehensive counseling to anticipate erratic bleeding prior to device insertion[5]. While many individuals may accept this irregular bleeding pattern, the associated discomfort could potentially impact their overall quality of life. The study found that conjugated equine estrogen could be considered as an alternative treatment option due to its characteristics of being user-friendly, having a shorter treatment duration, fewer side effects, and high efficacy in addressing uterine bleeding among users of contraceptive implants.

The strength of this study lies in its design as a randomized controlled trial with an appropriate sample size and an absence of dropouts. However, a limitation of the research is the lack of investigation into the duration of recurrent bleeding in patients, which could offer valuable insights for guiding patients in the selection of either of these two medications. Conducting further studies with extended follow-up periods could furnish additional information regarding the safety and efficacy of these treatments.

## Conclusion

Conjugated equine estrogen was more effective than mefenamic acid in controlling abnormal uterine bleeding associated with etonogestrel subdermal implants with low side effects and short duration of treatment. Hence, conjugated equine estrogen is a reasonable choice for treating the abnormal uterine bleeding side effects of hormonal subdermal implants.

## Acknowledgments

We thank (a) the participants for their cooperation, (b) the ward nursing staffs and physicians for their assistance, (c) the staff from the Obstetrics and Gynecology Department at Khon Kaen Hospital for their support, and (d) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript under the aegis of the Publication Clinic, Research Affairs, Khon Kaen University.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References

1. Croxatto HB. Progestin implants. Steroids 2000;65: 681-5.
2. Meirik O, Fraser IS, d'Arcangues C. Implantable contraceptives for women. Hum Reprod Update 2003;9:49-59.

3. Affandi B. Long-acting progestogens. Best Pract Res Clin Obstet Gynaecol 2002;16:169-79.
4. Archer DF, Philput CA, Weber ME. Management of irregular uterine bleeding and spotting associated with Norplant. Hum Reprod 1996;11(Suppl 2):24-30.
5. Friedlander E, Kaneshiro B. Therapeutic options for unscheduled bleeding associated with long-acting reversible contraception. Obstet Gynecol Clin North Am 2015;42:593-603.
6. Alvarez-Sanchez F, Brache V, Thevenin F, Cochon L, Faundes A. Hormonal treatment for bleeding irregularities in Norplant implant users. Am J Obstet Gynecol 1996;174:919- 22.
7. Phupong V, Sophonsritsuk A, Taneepanichskul S. The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use. Contraception 2006;73:253-6.
8. Schrager S. Abnormal uterine bleeding associated with hormonal contraception. Am Fam Physician 2002;65:2073-80.
9. Phaliwong P, Taneepanichskul S. The effect of mefenamic acid on controlling irregular uterine bleeding second to Implanon use. J Med Assoc Thai 2004;87:64–8.
10. Kaewrudee S, Taneepanichskul S, Jaisamraun U, Reinprayoon D. The effect of mefenamic acid on controlling irregular uterine bleeding secondary to Norplant use. Contraception 1999;60:25-30.
11. Upawi SN, Ahmad MF, Abu MA, Ahmad S. Management of bleeding irregularities among etonogestrel implant users: Is combined oral contraceptives pills or nonsteroidal anti-inflammatory drugs the better option? J Obstet Gynaecol Res 2020;46:479-84.
12. Hou MY, McNicholas C, Creinin MD. Combined oral contraceptive treatment for bleeding complaints with the etonogestrel contraceptive implant: A randomized controlled trial. Eur J Contracept Reprod Health Care 2016;21:361-6.
13. Belsey EM, Pinol EP. Menstrual bleeding patterns in untreated women. Contraception 1997;55:57–65.
14. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, et al. Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. Eur J Obstet Gynecol Reprod Biol 2010;152:133-7.
15. Intarangsri J,Puttasiri S. Bleeding Patterns after use of single-rod etonogestrel implant in postpartum adolescents. Thai J Obstet Gynaecol 2021; 29:322-30.
16. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a -pictorial chart. Br J Obstet Gynaecol 1990;97:734-9.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 295-305.

## GYNAECOLOGY

# Prevalence of Depressive Symptoms among Thai Reproductive-Aged Woman with Polycystic Ovary Syndrome and Associated Factors

Thanaree Achavangkool, M.D.*,
Thanyarat Wongwananuruk, M.D.*,
Somboon Hataiyusuk, M.D.**,
Panicha Chantrapnichkul, M.D.*,
Suchada Indhavivadhana, M.D.*,
Prasong Tanmahasamut, M.D.*,
Manee Rattanachaiyanont, M.D.*,
Kitirat Techatraisak, M.D.*,
Surasak Angsuwathana, M.D.*,
Nutchaya Sanga-areekul, BNS.*

** Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

## ABSTRACT

**Objectives:** This study aimed to determine the prevalence of depressive symptoms among Thai reproductive-aged woman with polycystic ovary syndrome (PCOS) and to identify factors associated with depression in this population.

**Materials and Methods:** A cross-sectional, questionnaire-based study was conducted at the Gynecologic Endocrinology Unit of Siriraj Hospital. The study enrolled women with PCOS between February 2022 and April 2023. The women were aged 18-45 years and met the revised Rotterdam 2003 criteria for PCOS. Participants with a prior psychiatric diagnosis or history of psychiatric medication use were excluded. Information was gathered about their background and recorded signs and symptoms of PCOS. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression and its severity. This study, scores of 9 or more indicated depressive disorder.

**Results:** A total of 193 PCOS women participated, with a mean age of 26.1 ± 5.4 years. Most participants exhibited oligomenorrhea (96.9%) and hyperandrogenism (93.8%). The prevalence of depression was 39.9%, with severity categorized as mild (28.0%), moderate (11.4%), and severe (0.5%). Univariate analysis identified that being a student, having no savings from income, the presence of acanthosis nigricans, and hyperandrogenism were significantly associated with depression. Multiple logistic regression analysis further revealed that only the absence of savings was significantly associated with depression in this population.

**Conclusion:** The prevalence of depression in Thai PCOS women, as categorized by the PHQ-9, was 39.9%. A lack of savings from income was a significant factor associated with depression in Thai reproductive women with PCOS.

**Keywords:** depression, PCOS, PHQ-9.

***Correspondence to:*** *Thanyarat Wongwananuruk, M.D., Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: thanyarat.won@mahidol.ac.th*

**Received:** 18 September 2023, **Revised:** 13 March 2024, **Accepted:** 18 March 2024

---

# *ความชุกของอาการซึมเศร้าในสตรีไทยวัยเจริญพันธุ์ที่เป็นกลุ่มอาการถุงน้ำรังไข่หลายใบและปัจจัยที่มีความสัมพันธ์*

***ธนารีย์ อัชวังกูล, ธันยารัตน์ วงศ์วนานุรักษ์, สมบูรณ์ หทัยอยู่สุข, ปณิชา จันทราพานิชกุล, สุชาดา อินทวิวัฒน์, ประสงค์ ตันมหาสมุทร, มณี รัตนไชยานนท์, กิติรัตน์ เตชะไตรศักดิ์, สุรศักดิ์ อังสุวัฒนา, ณัฐชญา สง่าอารีย์กุล***

## *บทคัดย่อ*

***วัตถุประสงค์****: การศึกษานี้จุดประสงค์เพื่อศึกษาหาความชุกของอาการซึมเศร้าในสตรีไทยวัยเจริญพันธุ์ที่เป็นกลุ่มอาการถุงน้ำรังไข่หลายใบ และเพื่อบ่งชี้ปัจจัยที่เกี่ยวข้องกับภาวะซึมเศร้าในกลุ่มประชากรนี้*

***วัสดุและวิธีการ****: การศึกษาแบบตัดขวางโดยใช้แบบสอบถามด้วยตนเองถูกทำที่หน่วยต่อมไร้ท่อทางนรีเวช โรงพยาบาลศิริราช การศึกษาได้รวบรวมสตรีที่เป็นกลุ่มอาการถุงน้ำรังไข่หลายใบ ในช่วงระหว่างเดือนกุมภาพันธ์ 2565 ถึง เมษายน 2566 สตรีมีอายุระหว่าง 18 ถึง 45 ปี และครบตามเกณฑ์ของ Revised Rotterdam 2003 สำหรับกลุ่มอาการถุงน้ำรังไข่หลายใบ ผู้เข้าร่วมวิจัยที่มีประวัติถูกวินิจฉัยโรคทางจิตเวช หรือมีประวัติใช้ยาจิตเวชจะถูกตัดออก ข้อมูลถูกรวบรวมเกี่ยวกับภูมิหลังของพวกเขาและข้อมูลบันทึกอาการแสดงและอาการของกลุ่มอาการถุงน้ำรังไข่หลายใบ แบบสอบถาม Patient Health Questionnaire (PHQ9) ถูกนำมาใช้เพื่อจัดแยกความผิดปกติและความรุนแรงของภาวะซึมเศร้า ในการศึกษานี้ คะแนนที่ 9 หรือมากกว่า บ่งชี้ความซึมเศร้าผิดปกติ

***ผลการศึกษา****: ทั้งหมดของ 193 คน ของสตรีที่เป็นกลุ่มอาการถุงน้ำรังไข่หลายใบเข้าร่วมการศึกษานี้ ด้วยอายุเฉลี่ย 26.1 ± 5.4 ปี ส่วนมากของผู้เข้าร่วมวิจัยมีรอบระดูห่าง (ร้อยละ 96.9) และมีอาการแสดงออกของฮอร์โมนเพศชายเกิน (ร้อยละ 93.8) ความชุกของภาวะซึมเศร้าคือ ร้อยละ 39.9 ด้วยการจัดแบ่งระดับความรุนแรง ระดับน้อย (ร้อยละ 28.0) ปานกลาง (ร้อยละ 11.4) และรุนแรง (ร้อยละ 0.5) การวิเคราะห์ข้อมูลแบบตัวแปรเดียวบ่งชี้ว่า การเป็นนักเรียน การไม่มีเงินเก็บจากรายได้ การมี acanthosis nigricans และการมีอาการแสดงออกของภาวะฮอร์โมนเพศชายเกิน เป็นความสัมพันธ์อย่างมีนัยสำคัญกับภาวะซึมเศร้า การวิเคราะห์พหุตัวแปรแสดงว่ามีเพียง การไม่มีเงินเก็บเป็นปัจจัยที่มีนัยสำคัญที่สัมพันธ์กับ*

*ภาวะซึมเศร้าในประชากรกลุ่มนี้*

***สรุป**: ความชุกของภาวะซึมเศร้าในสตรีไทยที่เป็นกลุ่มอาการถุงน้ำรังไข่หลาบใบ โดยใช้แบบสอบถาม PHQ-9 สำหรับการจัดแยก คือร้อยละ 39.9 การขาดแคลนงินเก็บจากงรายได้เป็นปัจจัยที่มีนัยสำคัญที่สัมพันธ์กับภาวะซึมเศร้าในสตรีไทยวัยเจริญพันธุ์ที่เป็นกลุ่มอาการถุงน้ำรังไข่หลายใบ*

***คำสำคัญ**: กลุ่มอาการถุงน้ำรังไข่หลายใบ, ภาวะซึมเศร้า, PHQ-9*

## Introduction

Polycystic ovary syndrome (PCOS) is a chronic disease of unknown origin that requires long-term management. The syndrome encompasses various physical and mental manifestations. They include menstrual abnormalities (oligomenorrhea or amenorrhea), abnormal sex hormone levels, hyperandrogenism (such as hirsutism, acne, and virilization), and a distinctive polycystic appearance of the ovaries on imaging. PCOS can have long-term health effects, including infertility; metabolic abnormalities such as obesity, insulin resistance, diabetes mellitus, and hypertension; and an increased risk of cardiovascular disease[1, 2]. Additionally, PCOS can lead to endometrial hyperplasia owing to unopposed estrogen from chronic anovulation, thereby increasing the risk of endometrial carcinoma. Collectively, these factors adversely affect patients' quality of life due to the exacerbation of negative perceptions of appearance (stemming from hyperandrogenism and obesity), infertility, and the potential for chronic health sequelae. Evidence reveals a more pronounced adverse emotional impact in PCOS women than in their non-PCOS counterparts, manifesting in disorders such as depression, anxiety, bipolar disorder, and binge eating disorder[3-5].

Major depressive disorder, commonly known as depression, is a psychiatric disorder characterized by depressed mood, loss of interest, and other symptoms, such as insomnia, decrease in appetite and recurrent thought of death, lasting the same 2-week period. The prevalence of depression in the general population ranges from 4% to 6%, with higher rates among women than men[3]. Among women with PCOS, the prevalence of depression varies widely, ranging from 17.3% to 76.7%, and increases with age[6-8]. Regional studies, such as those conducted in China, have identified a depression rate of 27.5% among women with PCOS, compared to only 13.3% in the general population[4]. Similar findings were observed in Australia, where the prevalence of depression was 18.8% in the general population but increased to 27.3% among women with PCOS[5]. Longitudinal studies conducted in Australia (with a 3-year follow-up period) and the United States (with a 2-year follow-up period) have shown a significant increase in the prevalence of depression and anxiety among women with PCOS[9, 10].

The Patient Health Questionnaire-9 (PHQ-9) was selected as the tool to assess and categorize depression in this study. The PHQ-9 is a validated and commonly used self-report questionnaire to screen for depression[11]. This tool is widely accepted for use in primary healthcare settings for screening and diagnosing depression[12]. It consists of 9 questions, each graded on a scale of 0–3, with a cumulative score exceeding 9 indicating the presence of major

depression. The PHQ-9 has been translated into a Thai version by Lotrakul et al, demonstrating a sensitivity of 84.0% and specificity of 77.0%[13]. However, the major depressive disorder should be diagnosed by psychiatrist including history, clinical evaluation and investigation for exclusion physical causes and evaluation severity of disorder by specific scale.

Given the higher likelihood of depression among women with PCOS, early mental health evaluation and intervention are advisable for this demographic. While numerous studies have been conducted in Western countries, no comparable research has been conducted in Thailand. Therefore, the primary objective of this study was to determine the prevalence of depression among Thai reproductive-age women with PCOS. The secondary objective was to identify the factors associated with depression in this population.

## Materials and Methods

This cross-sectional, questionnaire-based investigation was conducted at the Siriraj Gynecologic Endocrinology Unit from February 2022 to April 2023. Before this research began, its protocol was authorized by the Ethics Committee of the Siriraj Institutional Review Board (approval number 1102/2564 [IRB3]).

The study included women aged 18 to 45 years diagnosed with PCOS (based on the revised Rotterdam 2003 criteria) during the 6 months preceding the interview. These criteria require the presence of at least two of the following three conditions: oligomenorrhea or anovulation, hyperandrogenism or hyperandrogenemia, and polycystic ovarian morphology[1]. Proficiency in reading and writing Thai was also a requisite for inclusion. Participants were excluded if they had other diseases that could mimic PCOS, were pregnant or lactating, had previously been diagnosed with any psychiatric disorder or had history of psychiatric medication use.

The sample size calculation was based on a pilot study that used the PHQ-9 questionnaire to identify depression among PCOS patients. From pilot project which study in 20 women with PCOS (who attended in Gynecologic Endocrinological Unit, Siriraj Hospital) by using PHQ-9. The result showed the prevalence of PHQ-9 score > 9 scores were 5 women. Thus, the prevalence of depression in this pilot study was 25% (5/20). Using this formular n is number of participants, P is prevalence of depression (pilot study) = 0.25, $\alpha$ mean type I error = 0.05, 2- sided (95% confidence interval, Z = 1.96), d is margin of error = 0.0625 (25% of P). All values were put in the formular ($n = (1.96)^2 (0.25)(1- 0.25) / (0.0625)^2 = 184$). Adding incomplete data 5% = 9.2 women. Thus, the total participants was 193 women (184+9).

The PHQ-9 questionnaire served as a depression screening instrument, with permission to use the Thai version obtained from Lotrakul et al[13]. This questionnaire was sectioned into the following three parts: demographic and clinical profile: this section collected data on age, marital status, educational attainment, occupation, savings from income, obstetric history, underlying diseases, anthropometric measurements (weight, height, and waist circumference), and blood pressure. PCOS diagnosis: aligned with the revised Rotterdam 2003 criteria[1], this part of the questionnaire explored each patient's menstrual history, laboratory investigations, and signs of hyperandrogenism. Psychological evaluation: the third section comprised 9 items, with each item scored on a scale of 0 to 3. The total score ranged from 0 to 27. The scoring categories were 0–4 (normal), 5–8 (mildly depressed mood), 9–14 (mild major depression or dysthymia), 15–19 (moderate major depression), and ≥ 20 (severe major depression or major depressive disorder). For this study, scores of 9 or more indicated depressive disorder.

Before participating, patients were provided with information about the study's objective, the confidentiality of their data, and their right to accept or decline participation. Informed consent was obtained from all participants. Patients completed the questionnaires in a private room. Medical staff separately evaluated hyperandrogenism characteristics such as hirsutism (assessed using the modified Ferriman–Gallwey score), alopecia (assessed using Ludwig's score), and acne. Acanthosis nigricans was also recorded. Additionally, metabolic profiles were assessed via a 75-gram oral glucose tolerance test and lipid profile screening.

Data analyses were conducted using IBM SPSS Statistics, version 29 (IBM Corp, Armonk, NY, USA). Demographic data and characteristics were described using percentages, means, and standard deviations. The normal distribution of continuous data was confirmed using the Kolmogorov–Smirnov test. Independent t test was used to test continuous data. Univariable analysis was performed to identify factors associated with PHQ-9 questionnaire results, utilizing Fisher's exact test and the chi-square test. Multiple logistic regression analysis was employed to ascertain significant associated factors. The results were reported as odds ratios (OR), 95% confidence intervals (CIs), and p values.

## Results

A total of 266 women with PCOS who sought treatment at the Siriraj Gynecologic Endocrinology Unit were included in this study. After applying the exclusion criteria, 73 individuals were excluded (diagnosis time longer than 6 months: n = 41, incomplete laboratory report: n = 18, diagnosed with psychiatric disorder: n = 7, and diagnosed with PCOS-mimicking disorders: n = 7). Therefore, 193 women with PCOS were included in the analysis.

Table 1 presents the demographic data of the participants. Their mean age was 26.1 ± 5.4 years, and the mean body mass index (BMI) was 26.8 ± 7.5 kg/m$^2$, with most participants (49.7%) classified as obese. Approximately three-quarters of the participants (74.6%) had an undergraduate education. Regarding savings from income, 57.0% reported having savings, while 43.0% did not. Most participants were single (86%) and reported no need for fertility (91.2%). Acanthosis nigricans was observed in 30.1% of the population. The most common manifestations of PCOS were oligomenorrhea (96.9%) hyperandrogenism (93.8%), and polycystic ovarian morphology (52.8%). The most prevalent symptoms of hyperandrogenism were acne (77.2%), hirsutism (65.8%), and alopecia (40.4%).

Table 2 outlines the prevalence of depression. The overall prevalence of depression was 39.9% (28.0% categorized as mild major depression or dysthymia, 11.4% as moderate major depression, and 0.5% as severe major depression).

Table 3 presents the results of the univariable analysis. The findings revealed that being a student (OR 2.07, 95%CI 1.06–4.06), having no savings from income (OR 2.40, 95%CI 1.33–4.34), and the presence of acanthosis nigricans (OR 2.22, 95%CI 1.19–4.16) were associated with depression. Hyperandrogenism showed a significant correlation with depression (p = 0.02). However, no statistical correlation was observed between other clinical manifestations of PCOS and depression. When combining clinical manifestations, hyperandrogenism and oligomenorrhea showed a significant correlation (OR 3.66, 95%CI 1.02–13.12), whereas no other combinations correlated with depressive disorder.

After adjusting for confounding variables in the multivariable model (Table 4), only the factor of having no savings from income remained significantly associated with depression (adjusted OR 2.26, 95%CI 1.22-4.17).

**Table 1.** Demographic data of 193 Thai women with polycystic ovary syndrome.

| Characteristics | n (%) or mean ± SD |
|---|---|
| Age (years) | 26.1 ± 5.4 |
| BMI (kilogram/meter squared) | 26.8 ± 7.5 |
| Underweight | 14 (7.3) |
| Normal | 60 (31.1) |
| Overweight | 23 (11.9) |
| Obesity | 96 (49.7) |
| Waist circumference (centimeters) | 84.7±16.4 |
| Underlying disease | |
| Dyslipidemia | 4 (2.1) |
| Diabetes mellitus | 5 (2.6) |
| Hypertension | 6 (3.1) |
| Other | 25 (13.0) |
| Education | |
| Below undergraduate | 25 (13.0) |
| Undergraduate | 144 (74.6) |
| Postgraduate | 24 (12.4) |
| Profession | |
| Unemployed | 5 (2.6) |
| Student | 61 (31.6) |
| Freelance | 35 (18.1) |
| Officer | 92 (47.7) |
| Economic status | |
| No savings | 83 (43.0) |
| Savings | 110 (57.0) |
| Status | |
| Single | 166 (86.0) |
| Married | 26 (13.5) |
| Divorced | 1 (0.5) |
| Fertility needed | |
| No need | 176 (91.2) |
| Needed | 17 (8.8) |
| Presence of acanthosis nigricans | 58 (30.1) |
| Clinical presentation of PCOS | |
| Oligomenorrhea | 187 (96.9) |
| Hyperandrogenism | 181 (93.8) |
| Hirsutism | 127 (65.8) |
| Acne | 149 (77.2) |
| Alopecia | 78 (40.4) |
| PCOM | 102 (52.8) |

BMI: body mass index, n: number, PCOM: polycystic ovarian morphology, PCOS: polycystic ovary syndrome, SD: standard deviation
Underweight = BMI < 18.5 kg/m$^2$, Normal = BMI 18.5-22.9 kg/m$^2$, Overweight = BMI 23.0-24.9 kg/m$^2$, Obesity = BMI ≥ 25.0 kg/m$^2$

**Table 2.** Prevalence of depression in Thai women with polycystic ovary syndrome classified by PHQ-9.

| Severity of depression | n (%) |
|---|---|
| No depression | 116 (60.1) |
| Depression | 77 (39.9) |
| Mild | 54 (28.0) |
| Moderate | 22 (11.4) |
| Severe | 1 (0.5) |

PHQ-9: Patient Health Questionnaire-9, n: number
PHQ-9 scores 9–14 = mild major depression or dysthymia; scores 15–19 = moderate major depression; scores ≥ 20 = severe major depression.

**Table 3.** Unadjusted risk factor associated with depression in women with polycystic ovary syndrome.

| Factor | Depression | | Odds ratio (95%CI) | p value |
|---|---|---|---|---|
| | No (n = 116) | Yes (n = 77) | | |
| Age (years) | 26.6 ± 5.7 | 25.3 ± 5.0 | – | 0.091 |
| BMI | | | | |
| Underweight | 8 (6.9) | 6 (7.8) | 1.39 (0.43-4.55) | 0.583 |
| Normal | 39 (33.6) | 21 (27.3) | | |
| Overweight | 16 (13.8) | 7 (9.1) | 0.81 (0.29-2.29) | 0.694 |
| Obesity | 53 (45.7) | 43 (55.8) | 1.51 (0.77-2.93) | 0.227 |
| Central obesity | 111(95.7) | 75(97.4) | 1.69 (0.32-8.94) | 0.705 |
| Underlying disease | | | | |
| Dyslipidemia | 2 (1.7) | 2 (2.6) | 1.52 (0.21-11.03) | 1.000 |
| Diabetes mellitus | 3 (2.6) | 2 (2.6) | 1.00 (0.16-6.16) | 1.000 |
| Hypertension | 2 (1.7) | 4 (5.2) | 3.12 (0.56-17.49) | 0.219 |
| Education | | | | |
| Below undergraduate | 14 (12.1) | 11 (14.3) | 1.57 (0.49-5.01) | 0.445 |
| Undergraduate | 86 (74.1) | 58 (75.3) | 1.35 (0.54-3.36) | 0.520 |
| Postgraduate | 16 (13.8) | 8 (10.4) | 1.00 | |
| Profession | | | | |
| Unemployed | 2 (1.7) | 3 (3.9) | 3.43 (0.54-21.66) | 0.190 |
| Student | 32 (27.6) | 29 (37.7) | 2.07 (1.06-4.06) | 0.030* |
| Freelance | 64 (55.2) | 28 (36.4) | 2.16 (0.97-4.79) | 0.060 |
| Officer | 18 (15.5) | 17 (22.1) | 1.00 | |
| Economic status | | | | |
| No savings | 40 (34.5) | 43 (55.8) | 2.40 (1.33-4.34) | 0.004* |
| Savings | 76 (65.5) | 34 (44.2) | 1.00 | |
| Status | | | | |
| Single | 96 (82.8) | 70 (90.9) | 2.43 (0.93-6.37) | 0.071 |
| Married | 20 (17.2) | 6 (7.8) | 1.00 | |
| Presence of acanthosis nigricans | 27 (23.3) | 31 (40.3) | 2.22 (1.19-4.16) | 0.012* |
| Clinical presentation of PCOS | | | | |
| Oligomenorrhea | 113 (97.4) | 74 (96.1) | 0.66 (0.13-3.33) | 0.684 |
| Hyperandrogenism | 104 (89.7) | 77 (100) | NA | 0.020 |
| Hirsutism | 77 (66.4) | 50 (64.9) | 0.94 (0.51-1.73) | 0.836 |
| Acne | 85 (73.3) | 64 (83.1) | 1.80 (0.87-3.75) | 0.111 |
| Alopecia | 42 (36.2) | 36 (46.8) | 1.55 (0.86-2.78) | 0.144 |
| PCOM | 61 (52.6) | 41 (53.2) | 1.03 (0.58-1.83) | 0.928 |
| Oligomenorrhea and hyperandrogenism | 101 (87.1) | 74 (96.1) | 3.66 (1.02-13.12) | 0.035* |
| Hyperandrogenism and PCO | 54 (46.6) | 41 (53.2) | 1.31 (0.73,2.33) | 0.362 |
| Oligomenorrhea and PCOM | 58 (50) | 38 (49.4) | 0.97 (0.55-1.73) | 0.930 |
| Oligomenorrhea, hyperandrogenism, and PCOM | 51 (44) | 38 (49.4) | 1.24 (0.70-2.21) | 0.462 |

BMI: body mass index, CI: confidence interval, PCOM: polycystic ovary morphology, PCOS: polycystic ovary syndrome, NA: not applicable

* $p < 0.05$

**Table 4.** Adjusted factors associated with depression in women with polycystic ovary syndrome.

| Factor | Crude odds ratio (95%CI) | p value | Adjusted odds ratio (95%CI) | p value |
|---|---|---|---|---|
| Profession | | | | |
| Unemployed | 3.43 (0.54-21.66) | 0.19 | 3.24 (0.48-21.90) | 0.228 |
| Student | 2.07 (1.06-4.06) | 0.03 | 1.70 (0.84-3.42) | 0.141 |
| Freelance | 2.16 (0.97-4.79) | 0.06 | 1.67 (0.72-3.87) | 0.234 |
| Officer | 1 | | 1 | |
| No savings | 2.40 (1.33-4.34) | 0.004 | 2.26 (1.22-4.17) | 0.010* |
| Presence of acanthosis nigricans | 2.22 (1.19-4.16) | 0.012 | 1.73 (0.89-3.37) | 0.107 |
| Oligomenorrhea and hyperandrogenism | 3.66 (1.02-13.12) | 0.035 | 2.94 (0.79-10.93) | 0.108 |

CI: confidence interval
*$p < 0.05$

# Discussion

The prevalence of depression among Thai women with PCOS in this study was 39.9%, which was higher than that reported in the general population[3, 14]. In contrast, a study conducted in China reported a markedly lower depression prevalence of 27.5% among women with PCOS[4]. The higher prevalence observed in our study may be attributed to a larger proportion of participants experiencing hyperandrogenism, which can negatively impact self-esteem and mood[15]. Similarly, a study conducted in Australia revealed a depression prevalence of 27.3% among women diagnosed with PCOS[5]. This disparity in findings compared to our study may be attributed to population characteristics, particularly differences in economic status. As Thailand is classified as a developing country, it is plausible that the economic factors associated with such a classification could contribute to a heightened vulnerability to depression among women with PCOS. Additionally, it is crucial to acknowledge that variations in assessment tools or questionnaires utilized to assess depression may exist between studies, potentially influencing the reported prevalence rates.

However, women with PCOS in the United States have a higher rate of depression, with a prevalence of 53.0%[16], compared to other countries. The higher BMI among Americans could contribute to this discrepancy. In addition, the use of a self-reflective system to assess acne and hirsutism in the American study, instead of relying on a technician's evaluation, may have revealed a greater concern for external appearance and higher levels of body dissatisfaction.

Factors that could potentially moderate depression, such as age, underlying diseases, marital status, and desire for fertility were similar among the women with and without depression. However, the only significant factor associated with depression was the lack of savings from income; other factors, such as obesity or PCOS manifestations, showed no association. Obesity can impact self-esteem and may be related to hyperandrogenism. Treatment of obesity has been shown to reduce depression by improving body appearance[17]. Despite that obesity impact negatively on mood, promoting positive attitude on body-image are considered as protective factor in the context of depression and obesity. However, in the present investigation, no correlation between obesity and depression was found. Among the women who were obese, 55.8% were diagnosed with depression, whereas only 45.7% of those were not depressed. Nevertheless, the difference was nonsignificant (p =

0.227). This may be the result of positive self-imaging or it may not, further investigation is required. Univariate analysis revealed that hyperandrogenism and the clinical manifestation of oligomenorrhea were significantly associated with depression. These findings suggest that abnormal menstruation and a perceived feminine appearance strongly impact women's health and self-image.

As previously mentioned, women with PCOS are primarily characterized by hyperandrogenism, such as acne, hirsutism, and alopecia. These symptoms can have a negative impact on self-image, self-esteem, and overall quality of life and are often linked to a higher incidence of depression[15]. Our study showed that overall hyperandrogenism was related to depressive mood, as it caused concerns about external appearance and had a detrimental effect on self-esteem. Intriguingly, upon analyzing hyperandrogenism by subtype (acne, alopecia, and hirsutism), none of the subtypes revealed a correlation with the PHQ-9 score. This finding could be because some women with excessive hair growth in multiple body areas do not perceive it negatively or as limiting their self-concept[18]. Besenek et al[19] reported a positive correlation between serum free testosterone levels (an objective indicator of hyperandrogenism) and depression. However, another study found that clinical hyperandrogenism displayed no connection to biochemical hyperandrogenism in Thai women with PCOS[20].

Infertility can have an adverse impact on the emotional state and quality of life of women and their partners. However, due to the limited number of married women participating in our study, we could not demonstrate a statistically significant relationship between infertility and depression.

Being unemployed has a negative effect on one's financial or economic status. Beyond the monetary burden, unemployment engenders a crisis of identity and erodes self-esteem, both of which are additional sources of stress[21]. Consistent with previous research, our study found a strong association between having no savings from income and a negative mood. A prior study in Thai late pregnant women also demonstrated the adverse effects of not having enough money increased risk of antenatal depressive symptoms[22]. In the same way of this study which study in reproductive Thai PCOS women revealed no saving of income effect to depressive symptom. However, we did not find a correlation between unemployment and depression despite the expectation that there would be a comparable relationship. The number of unemployed individuals in our study may have been insufficient to yield statistically significant results.

Previous research has found that undergraduate and high school students tend to exhibit a high prevalence of negative emotions such as depression and anxiety. The potential factors behind this association include academic challenges and demands, satisfaction with interpersonal relationships, self-confidence, and even sleep quality[23, 24]. Similarly, in the current investigation, those who are undergraduate and high school student showed significant relation to depression. However, formal education level was not significantly associated with depression. Other factors, such as clinical symptoms and financial status, may impact patients more than education level.

Among women with PCOS, the incidence of newly diagnosed diabetes, hypertension, and dyslipidemia tends to be high. The potential impact of metabolic disorders on overall health and quality of life is a subject of concern. Numerous studies have explored the relationship between insulin resistance (IR) and psychological issues in women with PCOS. While an increased incidence of IR has been associated with feelings of anxiousness, the relationship with depression appears to be weak[25, 26]. Similarly, our study found no correlation between newly diagnosed metabolic diseases, particularly IR, and depression. This lack of correlation may be attributed to the short exposure to IR in some cases. Furthermore, some participants might not have received their laboratory results when they completed the questionnaire.

The presence of acanthosis nigricans, a skin lesion, is indicative of IR. Along with other physical appearance factors, it was previously hypothesized that such lesions could negatively impact self-esteem and overall satisfaction with external appearance. However, the present investigation found no discernible link between this skin condition and depression. This lack of association may be attributed to our cohort's limited exposure time of IR and acanthosis nigricans.

One limitation of this study was the characteristics of the participants, who were predominantly young adults, metropolitan workers, and single individuals, with only a small number of married women included. Consequently, factors such as fertility-related concerns could not be adequately assessed. About 1/3 of participants were student, thus, economic status might be dominated with no saving from income. Additionally, the study's participant pool was drawn from a single institution, potentially compromising its ability to fully represent the broader population of Thailand. Incorporating multiple institutions into the study design would allow for a more extensive and diverse subject pool, bolstering the study's robustness. It should also be noted that the PHQ-9 is a screening tool for the general population and may not be capable of being applied to a specific group. Future studies should be conducted in a multicenter setting and employ a subspecialty questionnaire tailored to the PCOS group. From sample size calculation, this study used high margin of error (25% of d value). Thus, the population number might be in lower limit to detect some significant associated factors.

Furthermore, this study was conducted in urban regions during the COVID-19 pandemic, a period of economic downturn. Notably, socioeconomic status is pivotal and significantly contributes to stress levels. The outcomes of subsequent studies might differ with improvements in the COVID-19 situation and the economic landscape.

This study represents the first investigation into the prevalence of depression among women with PCOS in Thailand. The prevalence was 39.9%, with 11.9% exhibiting moderate to severe depression. These values underscore the potential adverse implications for individuals grappling with depression. Furthermore, the findings highlight the importance of mental health evaluation among PCOS women and support the implementation of depression screening as a standard procedure for this group. Those with positive results particularly moderate to severe depression should be referred for professional evaluation.

## Conclusion

The prevalence of depression in Thai PCOS women, as categorized by the PHQ-9, was 39.9%. A lack of savings from income was a significant factor associated with depression in Thai reproductive women with PCOS.

## Acknowledgments

The authors express their sincere gratitude to Miss Nichamon Pingkul, our research assistant, for her valuable cooperation in participant recruitment and data collection. Additionally, the authors thank Miss Julaporn Pooliam for her support with the statistical analyses.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References

1. Rotterdam, ESRM, ASRM-Sponsored PCOS, consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
2. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.
3. Wang Y, Ni Z, Li K. The prevalence of anxiety and depression of different severity in women with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol 2021;37:1072-8.

4. Tan J, Wang QY, Feng GM, Li XY, Huang W. Increased risk of psychiatric disorders in women with polycystic ovary syndrome in southwest China. Chin Med J (Engl) 2017;130:262-6.
5. Damone AL, Joham AE, Loxton D, Earnest A, Teede HJ, Moran LJ. Depression, anxiety and perceived stress in women with and without PCOS: a community-based study. Psychol Med 2019;49:1510-20.
6. Kiejna A, Piotrowski P, Adamowski T, Moskalewicz J, Wciorka J, Stokwiszewski J, et al. [The prevalence of common mental disorders in the population of adult Poles by sex and age structure - an EZOP Poland study]. Psychiatr Pol 2015;49:15-27.
7. Kongsuk T, Supanya S, Kenbubpha K, Phimtra S, Sukhawaha S, Leejongpermpoon J. Services for depression and suicide in Thailand. WHO South East Asia J Public Health 2017;6:34-8.
8. Zenebe Y, Akele B, W/Selassie M, Necho M. Prevalence and determinants of depression among old age: a systematic review and meta-analysis. Ann Gen Psychiatry 2021;20:55.
9. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015;100: 911-9.
10. Kerchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study. Fertil Steril 2009;91:207-12.
11. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
12. Sun Y, Fu Z, Bo Q, Mao Z, Ma X, Wang C. The reliability and validity of PHQ-9 in patients with major depressive disorder in psychiatric hospital. BMC Psychiatry 2020;20:474.
13. Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC Psychiatry 2008;8:46.
14. Wang Y, Ni Z, Li K. The prevalence of anxiety and depression of different severity in women with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol 2021:1-7.
15. Cinar N, Kizilarslanoglu MC, Harmanci A, Aksoy DY, Bozdag G, Demir B, et al. Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome. Hum Reprod 2011;26:3339-45.
16. Pastore LM, Patrie JT, Morris WL, Dalal P, Bray MJ. Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women. J Psychosom Res 2011;71:270-6.
17. Hollinrake E, Abreu A, Maifeld M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril 2007;87:1369-76.
18. Pasch L, He SY, Huddleston H, Cedars MI, Beshay A, Zane LT, et al. Clinician vs self-ratings of hirsutism in patients with polycystic ovarian syndrome: Associations with quality of life and depression. JAMA Dermatol 2016;152:783-8.
19. Besenek M, Gurlek B. Hyperandrogenism in polycystic ovary syndrome affects psychological well-being of adolescents. J Obstet Gynaecol Res 2021;47:137-46.
20. Leerasiri P, Wongwananuruk T, Indhavivadhana S, Techatraisak K, Rattanachaiyanont M, Angsuwathana S. Correlation of clinical and biochemical hyperandrogenism in Thai women with polycystic ovary syndrome. J Obstet Gynaecol Res 2016;42: 678-83.
21. Almeshari WK, Alsubaie AK, Alanazi RI, Almalki YA, Masud N, Mahmoud SH. Depressive and anxiety symptom assessment in adults with polycystic ovarian syndrome. Depress Res Treat 2021;2021:6652133.
22. Phoosuwan N, Eriksson L, Lundberg PC. Antenatal depressive symptoms during late pregnancy among women in a north-eastern province of Thailand: Prevalence and associated factors. Asian J Psychiatr 2018;36:102-7.
23. Oliveira ES, Silva A, Silva K, Moura TVC, Araujo AL, Silva A. Stress and health risk behaviors among university students. Rev Bras Enferm 2020;73: e20180035.
24. Lun KW, Chan CK, Ip PK, Ma SY, Tsai WW, Wong CS, et al. Depression and anxiety among university students in Hong Kong. Hong Kong Med J 2018;24: 466-72.
25. Livadas S, Chaskou S, Kandaraki AA, Skourletos G, Economou F, Christou M, et al. Anxiety is associated with hormonal and metabolic profile in women with polycystic ovarian syndrome. Clin Endocrinol (Oxf) 2011;75:698-703.
26. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2017;32:1075-91.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 306-313.

## GYNAECOLOGY

# Validity and Reliability of Thai Version of the Overactive Bladder Questionnaire Short Form in Women with Overactive Bladder

Thanawat Sangnucktham, M.D.*,
Suvit Bunyavejchevin, M.D., MHS*,
Purim Ruanphoo, M.D.*

** Departments of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

## ABSTRACT

**Objectives:** To study the validity and reliability of Thai version of the overactive bladder questionnaire short form (OAB-q SF) and the correlation of Thai version OAB-q SF to Thai version overactive bladder questionnaire (OAB-q).

**Materials and Methods:** During December 2017 to February 2018, after Institutional Review Board (IRB) approvement, 46 Thai patients diagnosed as having overactive bladder (OAB) attending a Female Pelvic Medicine and Reconstructive Surgery clinic at King Chulalongkorn Memorial hospital were recruited. Patients' characteristics were recorded. The self- answered, Thai version of the OAB-q SF was administered on two occasions, at the day of recruitment and at 2 weeks apart (by mail). Thai version of OAB-q was administered only at the first visit.

**Results:** Mean ± standard deviation of age was 65.63 ± 11.64 years, and their mean body mass index (BMI=-0987 was 26.25 ± 8.13 kg/m$^2$. Most women were treated for OAB more than 6 months (47.9%). Behavioral modification was used to treat in all patients. Oral medication was administered in 54.35% of patients. Cronbach's alpha of the OAB-q SF was 0.80 and 0.93 for symptom-bother and health related quality of life (HRQL) domains, respectively. The intra-class correlation (ICCr) of symptom bother scale and HRQL were 0.90 and 0.94. The content validity index was equal to 1. Pearson correlation of the total score of the OAB-q SF and OAB-q was 0.95 for the first visit questionnaire.

**Conclusion:** Thai version of the OAB-q SF showed good psychometric properties (reliability and validity) for measuring the OAB symptom severity and HRQL. There was very strong correlation between Thai version of OAB-q SF and OAB-q.

**Keywords:** OAB-q SF, Overactive bladder, questionnaire.

***Correspondence to:*** *Suvit Bunyavejchevin, M.D., MHS, Female Pelvic Medicine and Reconstructive Surgery Division, Departments of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. E-mail: suvit.b@chula.ac.th*

**Received:** 16 February 2023, **Revised:** 3 October 2023, **Accepted:** 15 January 2024

# *ความตรงและความเที่ยงของแบบสอบถามกระเพาะปัสสาวะไวเกินฉบับสั้น (OAB-q SF) ในสตรีที่มีภาวะกระเพาะปัสสาวะไวเกิน*

***ธนวรรธน์ แสงนักธรรม, สุวิทย์ บุณยะเวชชีวิน, ปุริม เรือนภู่***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อศึกษาความตรงและความเที่ยงของแบบสอบถาม overactive bladder questionnaire short form (OAB-q SF) ฉบับภาษาไทยและความสัมพันธ์ของแบบสอบถาม OAB-q SF ฉบับภาษาไทยกับแบบสอบถาม overactive bladder questionnaire (OAB-q) ฉบับภาษาไทย*

***วัสดุและวิธีการ:*** *ระหว่างเดือนธันวาคม พ.ศ.2560 ถึง เดือนกุมภาพันธ์ พ.ศ.2561 หลังได้รับการอนุมัติจากกรรมการจริยธรรมแล้ว ทำการคัดเลือกผู้ป่วย 46 ราย ที่ได้รับการวินิจฉัยว่ามีภาวะกระเพาะปัสสาวะไวเกินที่มารับการรักษาที่คลินิกเวชศาสตร์เชิงกรานสตรีและศัลยกรรมซ่อมเสริมที่โรงพยาบาลจุฬาลงกรณ์ ทำการบันทึกลักษณะประชากร และให้ผู้ป่วยตอบแบบสอบถาม OAB-q SF ฉบับภาษาไทยด้วยตนเองสองครั้ง ในวันที่รับการคัดเลือกเข้าการศึกษา และอีกครั้งที่สองสัปดาห์ โดยส่งกลับทางไปรษณีย์ และทำการตอบแบบสอบถาม OAB-q ฉบับภาษาไทยเฉพาะวันที่รับการตรวจครั้งแรก*

***ผลการศึกษา:*** *ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตราฐานของอายุ คือ 65.63 ± 11.64 ปี และค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐานของดัชนีมวลกายคือ 26.25 ± 8.13 กิโลกรัมต่อตารางเมตร สตรีส่วนใหญ่ได้รับการรักษาภาวะกระเพาะปัสสาวะไวเกินมากกว่า 6 เดือน (ร้อยละ 47.9) ผู้ป่วยทุกคนได้รับการรักษาด้วยพฤติกรรมบำบัด และร้อยละ 54.35 ได้รับการรักษาด้วยยา ค่า Cronbach's alpha ของแบบสอบถาม OAB-q SF คือ 0.80 และ 0.93 ในโดเมน ความเดือดร้อนทางอาการและคุณภาพชีวิตที่เกี่ยวกับสุขภาพ ค่า intra-class correlation (ICCr) ของโดเมน ความเดือดร้อนทางอาการและคุณภาพชีวิตที่เกี่ยวกับสุขภาพ 0.90 and 0.94 ตามลำดับ ค่า Pearson correlation ของคะแนนรวมของแบบสอบถาม OAB-q SF และแบบสอบถาม OAB-q คือ 0.95 ในการตอบแบบสอบถามครั้งแรก*

***สรุป:*** *แบบสอบถาม OB-q SF ฉบับภาษาไทยมีผลทดสอบทางจิตวิทยา (ความเที่ยงและความตรง) อยู่ในเกณฑ์ดีในการวัดความรุนแรงของอาการภาวะกระเพาะปัสสาวะไวเกิน และคุณภาพชีวิตที่เกี่ยวกับสุขภาพ แบบสอบถาม OAB-q SF ฉบับภาษาไทยมีความสัมพันธ์กับแบบสอบถาม OAB-q ฉบับภาษาไทยอย่างมาก*

***คำสำคัญ:*** *OAB-q SF, กระเพาะปัสสาวะไวเกิน, แบบสอบถาม*

## Introduction

Overactive Bladder (OAB) is a common problem that impact health related quality of life (HRQL)[1]. OAB relates to embarrassment, depression, sleep disturbance and decreased sexual activity[2, 3]. The current definition of OAB is symptom complex consisting of urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, in the absence of infection or other obvious pathology[4]. Female gender is associated with a higher prevalence of OAB than male, particularly in younger people[5]. From study in 11 countries in Asia, the overall prevalence of OAB was 53.1% among adult women[6].

OAB is a symptoms-based condition. Patient-reported outcome (PRO) measurement is critical to provide more understandi ng of the condition's impact. To be appropriate for evaluation of patients' condition, PROs must be supported by evidence of reliability, validity, and responsiveness. Moreover, PROs should be easy and practical to administer[7, 8]. The overactive bladder qQuestionnaire (OAB-q) is a multi-dimension instrument designed to assess patient perception of symptom bother and impact on HRQL among patients with OAB. The OAB-q consists of an 8-item symptom bother scale and a 25-item HRQL scale covering 4 domains: coping, concern, sleep and social interaction[9]. The OAB-q has been shown to be reliability, validity and responsiveness to change among OAB patients[9-11]. The OAB-q was originally developed in United States in English and has been translated into Thai language[12]. However, the 33-item OAB-q is not usually practical due to clinician and patient burden. A shorter version of instrument should be used to reduce respondent burden. The overactive bladder questionnaire-short form (OAB-q SF) is a brief, self-administered PRO tool with two scales assessing symptom bother and HRQL in patients with OAB[13]. The OAB-q SF captures the full spectrum of OAB symptom bother and HRQL impact with good reliability, validity and responsiveness, while being less time-consuming for patients to complete[3].

The aims of this study were to test the validity and reliability of Thai version of the OAB-q SF and to test the correlation of Thai version of the OAB-q SF to Thai version of the OAB-q.

## Materials and Methods

This prospective study was conducted at the Female Pelvic Medicine and Reconstructive Surgery Unit, Department of Obstetrics and Gynecology, King Chulalongkorn Memorial hospital during the December 2017 to February 2018 study period. The study protocol was approved by the Institutional Review Board of the university (COA 962/2017). Fifty women who were diagnosed as having OAB were recruited. The inclusion criteria were women who were ≥ 18 years of age, diagnosed as having the symptoms of OAB (diagnosis criteria for OAB: having urinary frequency, urgency with or without urge urinary incontinence for ≥ 3 months and at least one episode of urgency with or without incontinence in the last 3 days), and able to complete the 3-days bladder diary correctly (for the evidence of the urgency episodes and rule out other causes of urinary frequency such as polydipsia). Exclusion criteria were stress urinary incontinence or mixed-type urinary incontinence, patient with indwelling catheters or practicing intermittent self-catheterization, evidence of symptomatic urinary tract infection, previous pelvic radiation therapy, previous or current malignant disease of the pelvic organs, diabetic neuropathy, and bladder stones. Informed consents were obtained in all cases.

### OAB-q[9]

The OAB-q consists of 33 questions, which are grouped into two parts. The first part consists of eight questions which construct the symptom bother subscale and concern the severity of the patient's symptoms (frequency, urgency, nocturia and urgency incontinence). This subscale score varies from 0 and 100. The higher the symptom bother score is, the greater the bother from the overactive bladder symptoms. The second OAB-q part consists of 25 questions and measures HRQL with four subscales

(scores from 0 to 100). The higher the HRQL score, the better the HRQL level is. For these four subscales, the higher the score is, the less the subscale is affected by the disease. The OAB-q had been translated into Thai[12]. The Thai version of OAB-q had the good reliability and consistency with intraclass correlation (ICCr) of 0.97 and Cronbach's Alpha coefficient of 0.95[12].

**OAB-q SF**[13]

The OAB-q SF is a 19-item, self-administered, and disease specific instrument derived from the OAB-q[12]. The OAB-q SF contains two main subscales: symptom bother (6 items) and health-related quality of life (HRQL, 13 items). Each item is rated on a six-point likert scale. The symptom bother scale ranges from 0 (not at all) to 6 (a very great deal) and the HRQL scale ranges from 0 (none of the time) to 6 (all of the time). The two subscales are separately summed and transformed into scores ranging from 0 to 100. A higher score on the symptom bother scale indicates a greater symptom severity and a higher score on the HRQL scale indicates a better HRQL, so they are inversely related to each other. These two scores are mentioned separately (the OAB-q SF has no total score).

**Translation process**

After permission from the original study's authors, the English version of OAB-q SF was forward translated into Thai language by a linguist from Language institute of a Thai university and backward translated by another linguist. To confirm the content validity of the Thai version, the questionnaire was evaluated face-to-face with five patients who diagnosed with OAB visiting the Female Pelvic Medicine and Reconstructive Surgery outpatient clinic with another content validation by the 2 urogynecologists. Both urogynecologists read all 19 item questions and check whether the questions were valid (Thai version questions had the same meaning corresponding to the original English version, Thai version measured what the original questionnaire intended to measure). If any question were not agreed by any urogynecologists. That questions were sent back for re-translation and repeated the questionnaire development process again. All 19 items had to be agreed (valid) by both urogynecologists. So, the content validity index was equal to 1.

The Thai version of the OAB-q SF and Thai version of the OAB-q questionnaires were distributed to all participants by the research nurse. The questionnaires were self-answered twice (at 0 and 2 weeks). Test-retest reliability was examined using the intra-class correlation (ICCr) and Cronbach's alpha between first and second applications of the questionnaires. Pearson correlation coefficients (r) was used to test the correlation of Thai version of the OAB-q SF and Thai version of the OAB-q. The sample size was calculated from a pilot study (10 women who diagnosed with OAB, answering the questionnaires two time with 2 weeks interval), using the intra-class correlation of Thai version of the OAB-q SF from the pilot study (ICCr = 0.88, acceptable error: 10% of p value = 0.05)[14]. The sample size required was 41 cases. Nine cases (20%) were added to account for the lost to follow-up cases. The total sample size required was 50 cases.

Statistical analysis was performed using SPSS software version 22.0 (SPSS science, Chicago, IL, USA). Cronbach's Alpha coefficient was used to measure the internal consistency of Thai version of the OAB-q SF. An intraclass correlation (ICCr) was used to measure the test-retest reliability of Thai version of the OAB-q SF and the correlation with Thai version of the OAB-q.

# Results

Fifty participants were recruited, all accepted to participate in the study and provided their written informed consent to participant in the study. Four participants were excluded because they did not send back the questionnaires. The mean ± standard deviation for age, body mass index (BMI) and parity were 65.63 ± 11.64 years, 26.25 ± 8.13 kg/m$^2$ and 2.0 ±1.35, respectively (Table 1). Almost half of participants

(22 cases (47.83%)) were treated more than 6 months. Behavioral therapy was used in all patients whereas only 25 cases (54.35%) were treated with medication. For Thai version of the OAB-q SF, Cronbach's alpha internal consistency index attained a value of 0.80 in symptom bother scale and 0.931 in HRQL scale. The mean ± standard deviation for first and second visit score were 37.63 ± 19.24, 37.25 ± 20.33 in symptom bother scale and 72.82 ± 19.73, 73.0 ± 20.93 in HRQL scale. The ICCr of symptom bother scale and HRQL were 0.90 and 0.94 (Table 2.)

Pearson correlation of the total score in Thai version of the OAB-q SF and Thai version of the OAB-q was 0.95 for the first visit questionnaire (Fig. 1).

**Table 1.** Demographic data (n = 46 participants).

| Characteristics | mean ± SD |
|---|---|
| Age (years) | 65.63 ± 11.64 |
| BMI (kg/m$^2$) | 26.25 ± 8.13 |
| Parity | 2.0 ± 1.35 |
| | **n (%)** |
| Underlying disease | |
| Diabetes mellitus | 7 (15.21) |
| Essential hypertension | 25 (54.35) |
| Neurological disease | 3 (6.52) |
| Education | |
| Less than high school | 11 (23.91) |
| High school | 15 (32.61) |
| Bachelor degree | 16 (34.78) |
| Master degree and higher | 4 (8.69) |
| Duration of OAB treatment | |
| Less than 1 months | 10 (21.74) |
| 1-3 months | 11 (23.91) |
| 3-6 months | 3 (6.52) |
| More than 6 months | 22 (47.83) |
| Type of treatment | |
| Behavioral therapy | 46 (100) |
| Bladder training | 42 (91.30) |
| Medication | 25 (54.35) |

SD: standard deviation, BMI: body mass index

**Table 2.** Demographic data (n = 46 participants).

| Subscale | Cronbach's alpha | First visit score (mean ± SD) | Second visit score (mean ± SD) | Intra-class correlation |
|---|---|---|---|---|
| Symptom bother | 0.80 | 37.63 ± 19.24 | 37.25 ± 20.32 | 0.90 |
| HRQL | 0.93 | 72.82 ± 19.73 | 73.02 ± 20.93 | 0.94 |

SD: standard deviation, HRQL: health related quality of life

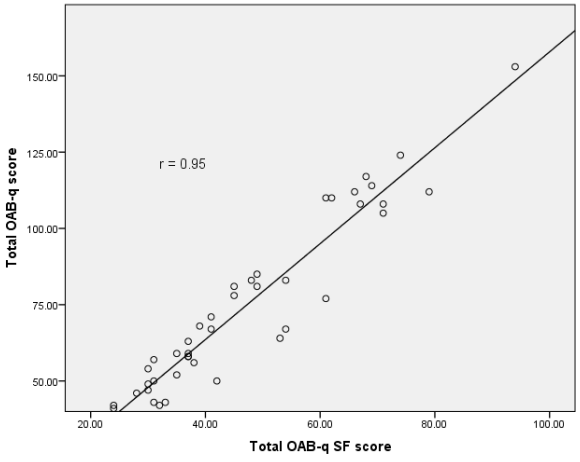


Fig. 1. Pearson correlation (r) between Thai version OAB-q SF and Thai version OAB-q score.

## Discussion

OAB is chronic medical condition and complex symptoms. To evaluate the severity of symptoms may need a long time. A good questionnaire can decrease the time in clinical setting. The questionnaire must brief, easy to complete, precise and reliable. The OAB-q SF fulfills these criteria[13]. This study reported on psychometric properties of Thai version of the OAB-q SF. The internal consistency (Cronbach's alpha) was in the acceptable range (more than 0.7[15] and the test-retest reliability was in the excellent range (more than 0.9)[16]. In addition, Pearson correlation between the total score of Thai version of the OAB-q SF and Thai version of the OAB-q was in the very strong correlation range[17].

The primary objective of this study was to translate and validate the OAB-q SF in the Thai language. The results of this study showed that this Thai version was valid, reliable. This enables the use of the OAB-q SF in daily practice in Thailand. This valid tool can be used to measure symptom bother and quality of life in patients with OAB with less items than the original OAB-q.

The results of this study were used to compare the psychometric study of the OAB-q SF in English[13] and Spanish versions[18]. Cronbach's alphas of English and Spanish version attained 0.81 and 0.81 in symptom bother scale and 0.92 and 0.92 in HRQL. Intra-class correlation was 0.92 and 0.86[13,18]. The psychometric properties of Thai version of the OAB-q SF were similar to original and Spanish version. Concerning the criterion validity, the present study used the Thai version OAB-q to correlate with the Thai OAB-q SF because we would like to compare the Thai OAB-q SF to the original version (gold standard). Because the original version has many questions that take long time to complete the questionnaires. Shorter version with similar reliability and validity can increase the use of this questionnaire in clinical and research setting.

For clinical application, Thai version of the OAB-q SF is shorter than the original version (OAB-q) to use in an outpatient department. It may alert the physician to closely evaluate symptoms in the patient who has severe symptoms with the high impact on quality of life. This Thai version of OQB-q SF can also be used in research to compare with other studies in OAB treatment for Thai women in the future.

### Strengths of this study

This study was conducted with the strict validation process with the development process fully compatible with standard protocol suggested by the ISPOR ( international Society for Pharmacoeconomics and Outcome Research) task force for translation and cultural adaptation[19]. The questionnaire translation

was done by experienced linguists. The inclusion criteria of this study were strict and clear. All participants must complete 3-day bladder diary for diagnosis OAB.

**Limitation of this study**

The study of responsiveness was not included in our study. Therefore, further studies of Thai version of OAB-q SF in women before and after the treatment comparing to clinical symptoms such as voiding diary are advocated.

# Conclusion

Thai version of the OAB-q SF showed good psychometric properties (reliability and validity) for measuring the OAB symptom severity and HRQL. Thai version of the OAB-q SF had very strong correlation to Thai version of the OAB-q. We recommend the use of this questionnaire in both research and clinical practice.

# Potential conflicts of interest

The authors declare no conflicts of interest.

## References


1. Garnett S, Swithinbank L, Ellis-Jones J, Abrams P. The long-term natural history of overactive bladder symptoms due to idiopathic detrusor overactivity in women. BJU Int 2009;104:948–53.
2. Coyne KS, Sexton CC, Kopp ZS, Ebel-Bitoun C, Milsom I, Chapple C. The impact of overactive bladder o mental health, work productivity and health-related quality of life in the UK and Sweden: Results from EpiLUTS. BJU Int 2011;108:1459-71.
3. Coyne KS, Sexton CC, Thompson C, Kopp ZS, Milsom I, Kaplan SA. The impact of OAB on sexual health in men and women: Results from EpiLUT. J Sex Med 2011:8:1603-15.
4. Abrams P, Artibani W, Cardozo L, Dmochowski R, van Kerrebroeck P, Sand P. Reviewing the ICS 2002 terminology report: the ongoing debate. Neurourol Urodyn 2009;28: 287.
5. Coyne KS, Sexton CC, Bell JA, Thompson CL, Dmochowski R, Bavendam T, Chen CI, Quentin Clemens J. The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. Neurourol Urodyn 2013;32:230-7.
6. Lapitan MC, Chye PLH. Asian-Pacific Continence Advisory Board. The epidemiology of overactive bladder among females in Asia: a questionnaire survey. Int Urogynaecol J 2011;12:226-31.
7. FDA. Guidance for Industry: Patient-reported outcome measures – Use in medical product development to support labeling claims. In: Office of the Federal Register, National Archives and Records Administration. Federal Register. Washington, DC: Food and Drug Administration 2009:65132-3.
8. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008;61:102-9.
9. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, Kurth H, Abrams P. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. Qual Life Res 2002;11:563-74.
10. Coyne KS, Matza LS, Thompson C, Jumadilova Z, Bavendam T. The responsiveness of the OAB-q among OAB patient subgroups. Neurourol Urodyn 2007;26: 196-203.
11. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: The overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). Neurourol Urodyn 2005;24: 215-25.
12. Bunyavejchevin S, Liao L, Lu SH, Choo MS, Rabbani KJ, Havanond P. Should we use the shorter Thai-version quality of life and symptoms questionnaires in women with overactive bladder. J Obstet Gynecol Res 2015;41:1260-65.
13. Coyne KS, Thompson CL, Lai JS, Sexton CC. An overactive bladder symptom and health-related quality of life short-form: Validation of the OAB-q SF. Neurourol Urodyn 2015;33:255-63.
14. Zou GY. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. Stat Med 2012;31:3972-81.
15. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ 2011;27:53-55.
16. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15:155-63
17. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. Anesth

Analg 2018;126:1763-8.
18. Arlandis S, Ruiz MA, Errando C, Villacampa F, Arumí D, Lizarraga I, et al. Quality of life in patients with overactive bladder: Validation and psychometric properties of the Spanish overactive bladder questionnaire-short form. Clin Drug Investig 2012; 32: 523-32.
19. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR task force for translation and cultural adaptation. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health 2005;8:94-104.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 314-319.

## CASE REVIEW

# Mesonephric-like Adenocarcinoma Arising from the Ovary: A Case Review and Treatment Considerations

Yu Horibe, Ph.D*,
Toshiyuki Kanno, Ph.D*,
Takashi Motohashi, Ph.D*,
Yosika Akizawa, Ph.D*,
Hiroshi Funamoto, Ph.D*,
Tsutomu Tabata, Ph.D*,

** Department of Obstetrics and Gynecology, Tokyo Women's Medical University, Tokyo, Japan*

## ABSTRACT

Mesonephric-like adenocarcinomas (MLAs) are a rare classification of pathologic cancers. These clinically high-grade cancers exhibit a distinct propensity for distant metastasis, notably in the lungs, often diagnosed at advanced stages (II–IV) according to The International Federation of Gynecology and Obstetrics (FIGO), and clinical course is unclear. A 62-year-old woman was diagnosed as a left ovarian tumor, magnetic resonance imaging (MRI) revealed a 68 mm nodule confined to the left ovary with no evidence of pelvic cavity invasion. After surgery, the patient was diagnosed with FIGO stage IIIA1(ii) mesonephric-like adenocarcinoma. Homologous recombination deficiency (HRD) status and breast cancer 1/2 (*BRCA1/2*) were negative. Postoperatively, the patient received six sessions of taxotere and cyclophosphamide (TC) chemotherapy as an adjuvant chemotherapy with no recurrent lesions. There are few reports that the positive rate of HRD score and the efficacy of poly adenosine diphosphate (ADP) - ribose polymerase inhibitors (PARPi) remain unclear. Adjuvant chemotherapy using carboplatin and paclitaxel after complete surgery has shown promising results with a low risk of recurrence. Further accumulation of cases and studies on regimens, including long-term prognosis and maintenance therapy are needed.

**Keywords:** Mesonephric-like adenocarcinoma, ovarian malignancy, pathological classification, prognosis, adjuvant chemotherapy.

***Correspondence to:*** *Yu Horibe, Ph.D., Tokyo Women's Medical University, Department of Obstetrics and Gynecology, Kawada-cho, Shinjuku-ku, Tokyo, Japan. Email: doyouknowphy@gmail.com*

**Received:** 28 September 2023, **Revised:** 10 October 2023, **Accepted:** 7 November 2023

## Introduction

Mesonephric-like adenocarcinomas (MLAs) are a rare classification of pathologic cancers, initially reported in 2016. These clinically high-grade cancers exhibit a distinct propensity for distant metastasis, notably in the lungs. This new variant of epithelial tumors has been included in the 5th edition of the World Health Organization's (WHO) recent 2020 classification of female genital cancers[1-3].

The term "like" is used because mesonephric-like adenocarcinoma (MLA) frequently occurs in the uterine body and ovaries without the presence of mesonephric remnants. It exhibits morphologic, immunophenotypic, and molecular features that overlap with mesonephric adenocarcinoma, which typically arises from normal or hyperplastic mesonephric remnants and is predominantly found in the lateral wall of the cervix. Thus, MLA shares similar characteristics with mesonephric adenocarcinoma and originates from mesonephric remnants.

MLA is often diagnosed at advanced stages (II–IV) according to the International Federation of Gynecology and Obstetrics (FIGO), with a tendency toward early recurrence and distant metastasis[3].

The pathological features of MLA included multiple structural patterns, such as tubular, glandular, pseudoendometrial, tubular, papillary, and full. Immunostaining demonstrated positive results for GATA binding protein 3 (GATA3), thyroid transcription factor 1 (TTF1), cluster of differentiation 10 (CD10), and paired box protein-8 (PAX8), but was negative for estrogen, other hormone receptors, and Wilms' Tumor Gene 1 (WT1). Additionally, wild type p53 was expressed. Other notable features included luminal eosinophilic colloidal material, dense or vesicular chromatin, inconspicuous nucleoli, nuclear densities, and an absence of squamous or mucous differentiation[4]. MLA represents an extremely rare ovarian malignancy, with only a limited number of case reports documented worldwide. Consequently, the clinical course, chemotherapy sensitivity, and efficacy of treatment for MLA remain unclear. In this report, we described a case of ovarian malignancy diagnosed as an MLA, including insights into the course of treatment.

## Case

A 62-year-old woman (para 1-0-0-1) with bronchial asthma consulted a gynecologist who diagnosed her with a left ovarian tumor measuring approximately 6 cm. She visited our hospital for the first time a week later. Prior to this visit, she had not sought gynecological care for over 10 years.

Magnetic resonance imaging revealed a 68 mm nodule confined to the left ovary with no evidence of pelvic cavity invasion (Fig. 1). No other abnormal findings were observed on cervical and endometrial cytology. Blood tests showed an elevated cancer antigen 125 (CA125) level of 86 U/mL, while carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9) levels were within the normal range. We decided that if the intraoperative rapid histological diagnosis indicated malignancy, we would perform a total abdominal hysterectomy, bilateral adnexectomy, pelvic lymph node dissection, para-aortic lymph node dissection, and oophorectomy.

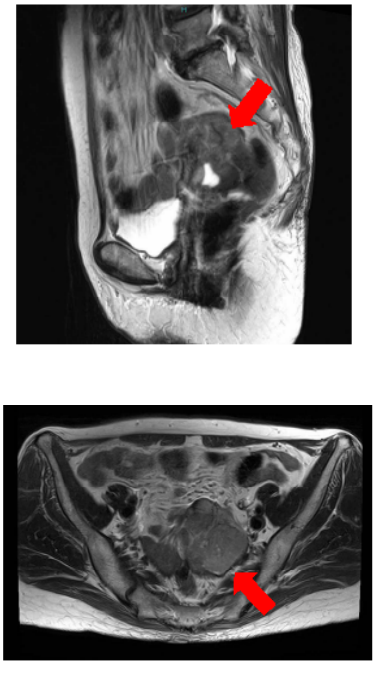

**Fig. 1.** Magnetic resonance imaging.
A substantial nodule is localized within the left ovary with no findings suggesting invasion into the pelvic cavity.

During the intraoperative examination, a minute amount of ascites was noted, and the left ovary appeared enlarged and swollen to the size of a clenched fist. However, the surface of the ovary was smooth without any signs of collapse. Additionally, a solitary enlargement of the para-aortic lymph node in the B1 region was observed.

Initially, left adnexectomy was performed, and a rapid pathological diagnosis confirmed the malignancy of the tumor. Consequently, a comprehensive surgical procedure, including total abdominal hysterectomy, bilateral adnexectomy, pelvic lymph node dissection, para-aortic lymph node dissection, and oophorectomy, was completed. The postoperative course was uneventful, and the patient was discharged on the seventh postoperative day. The intraoperative ascites cytology yielded a negative result. Moreover, the pathology of the left ovary revealed atypical cells forming glandular luminal structures, cribriform structures, and proliferative cells. The lumen exhibited an accumulation of highly acidic material, and necrotic lesions were also observed. Immunostaining results indicated a positive expression of PAX8 with CD10 observed on the luminal surface. The thyroid transcription factor-1 (TTF-1) showed weak to extensive positive staining, p53 expression was consistent with the wild-type status, and estrogen receptor (ER), progesterone receptor (PgR), Wilms' tumor protein (WT-1), GATA3, calretinin, and inhibin staining showed negative results. In addition, a solitary metastasis was identified in the B1 region of the para-aortic lymph nodes (Fig. 2 and 3). As a result, the patient was diagnosed with FIGO stage IIIA1(ii) mesonephric-like adenocarcinoma. Postoperatively, the patient received six sessions of carboplatin and paclitaxel (TC) chemotherapy (175 mg/$m^2$, AUC 6) as an adjuvant chemotherapy. As complication, the patient developed severe peripheral neuropathy. At present day, one year has passed since the initial surgery without recurrence and peripheral neuropathy is showing signs of mild improvement.

In addition, Myriad Mychoice Test® was performed for homologous recombination deficiency (HRD) search, Myriad HRD status was negative (patient genomic instabolity score was 1 point) and tumor mutation breast cancer 1 (BRCA1) / breast cancer 2 (BRCA2) status was negative.

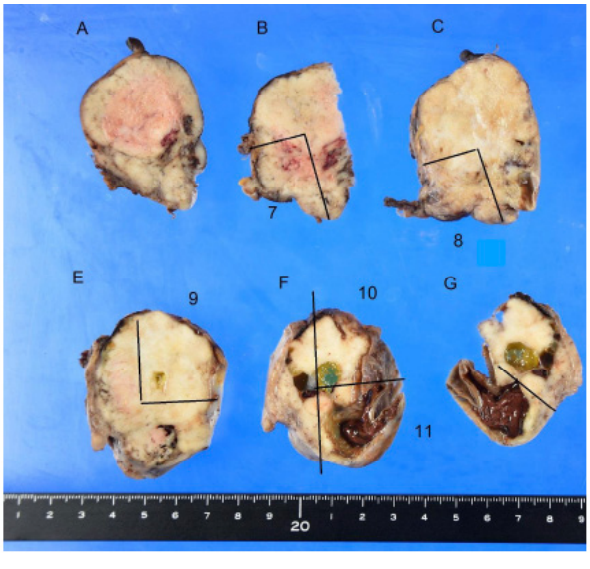


**Fig. 2.** The gross Findings.

Atypical cells form and proliferate in glandular luminal and cribriform structures. Within the lumen, there is an accumulation of acidophilic material. Necrosis is observed. Adjacent to this lesion are multiple cystic lesions. The cyst wall is mainly encapsulated by a single layer of epithelium, but shows partial papillary growths, some of which are contiguous with the above lesions.

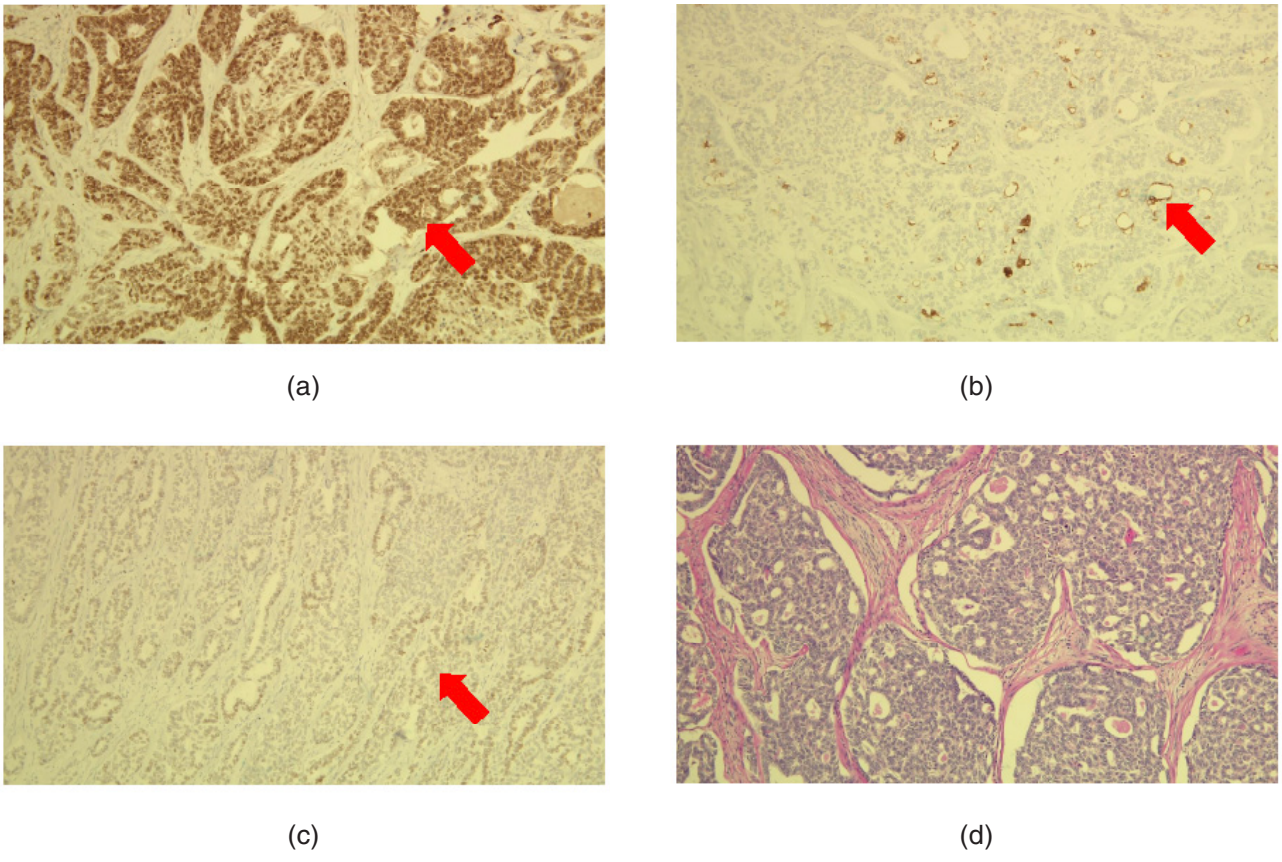


**Fig. 3.** Pathologic findings.
(a) PAX8 positive, (b) CD10 positive on luminal surface, (c) TTF-1 weakly to extensively positive, (d) hematoxylin and eosin stain

## Discussion

Due to its recent addition to the WHO classification in 2020, there are limited available reports on MLA, which is a new pathological classification of ovarian malignancies. It arises from transdifferentiation of the mesonephric remnants of the parenchymal ovarian tissue or from benign or neoplastic Müllerian duct precursors. Furthermore, other genetic MLAs have been reported to have a very high frequency of Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations, followed by Phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutations[5].

Clinically, MLA is often diagnosed at stages I–II in unilateral ovaries, although a considerable number of cases are detected at stages II–IV. Reports indicate that lung metastasis is the most common in advanced stages of ovarian cancer[6]. Furthermore, the tumor marker CA125 tends to increase as the advanced ovarian cancer progresses[7].

In terms of prognosis, MLA of ovarian origin has a worse prognosis compared with low-grade serous carcinoma and is similar to that of high-grade serous carcinoma (HGSC). Thus, MLA should be treated as a high-grade tumor, similar to high-grade serous carcinoma and clear cell carcinoma[4]. On the other hand, as a result that Myriad HRD Status was negative (patient genomic instability score was 1 point) and tumor mutation *BRCA1*/*BRCA2* Status was negative, compared to HGSC, chemotherapy including TC chemotherapy may be effective, while its efficacy against poly adenosine diphosphate (ADP) -ribose polymerase inhibitors is still unknown.

In a multicenter study by Jennifer, a 5-year

progression-free survival of 68% and overall survival of 71% were reported in 23 patients. The most common sites of recurrence were the lung (40%, 2/5) and omentum (40%, 2/5). However, many aspects of MLA remain unclear, and a larger study including the efficacy of post-therapy is warranted[6].

In a report on chemotherapy after surgical therapy, adjuvant chemotherapy was administered to four patients with stage IC-II tumors. Among the four patients, three had no recurrences based on available follow-up information. In contrast, patients with stage IA disease who did not receive adjuvant chemotherapy experienced multiple metastatic relapses approximately 13 months after surgery. Although the number of reports is limited, they suggest that sensitivity to chemotherapy may be favorable[7]. Conversely, Qiuhe et al recommended carboplatin and paclitaxel as the first-line chemotherapy of choice for MLA. However, they stated that the prognosis was poor[8].

There have been two reported cases of MLA arising from endometriosis[9] and one from a serous borderline tumor[10]. These findings suggested the potential involvement of precancerous lesions in the development of MLA. Although there was no history of MLA in our case, this possibility should be considered. However, it may be difficult to distinguish MLA from endometrial carcinoma pathologically, and morphological and immunohistochemical features should be examined. The diagnostic challenge associated with MLA may lead to diagnostic errors, potentially leading to the misclassification of patients as having low-grade neoplasms with a favorable prognosis, or vice versa[2]. Therefore, gynecologists and pathologists should actively consult and scrutinize these immunostains in the presence of clinically and pathologically non-specific conditions.

However, it is important to acknowledge the limitation of our current knowledge on MLA, as there is a scarcity of large case reports due to its rarity and novelty. The pathological diagnosis of MLA is often extremely challenging, carrying a potential risk of overlooked diagnoses.

# Conclusion

Based on several case reports, adjuvant chemotherapy using a combination of two drugs, namely carboplatin and paclitaxel, after complete surgery has shown promising results with a low risk of recurrence. However, the positive rate of homologous recombination deficiency and the efficacy of poly ADP-ribose polymerase inhibitors remain unclear. Further accumulation of cases and studies on regimens, including long-term prognosis and maintenance therapy, are needed to enhance our understanding of MLA.

# Potential conflicts of interest

The authors declare no conflicts of interest.

## References


1. Turashvili G, Lastra R. What's new in gynecologic pathology 2021: ovary and fallopian tube. J Pathol Transl Med 2021;55:366-7.
2. Restaino S, Pellecchia G, Tulisso A, Paglietti C, Orsaria M, Andreetta C, Poletto E, et al. Mesonephric-like adenocarcinomas: A rare tumor—the importance of diagnosis. Int J Environ Res Public Health 2022;19:14451.
3. Ma T, Chai M, Shou H, Ru G, Zhao M. Mesonephric-like adenocarcinoma of uterine corpus: A clinicopathological and targeted genomic profiling study in a single institution. Gynecol Oncol 2022;12:911695.
4. Buza N. Immunohistochemistry in gynecologic carcinomas: Practical update with diagnostic and clinical considerations based on the 2020 WHO classification of tumors. Semin Diagn Pathol 2022;39:58-77.
5. Liu Y, Karnezis A. Mesonephric-like adenocarcinoma: Two cases of a rare entity and review of literature. Am J Clin Pathol 2020;154:S59.
6. Pors J, Segura S, Chiu DS, Almadani N, Ren H, Fix DJ, et al. Clinicopathologic characteristics of mesonephric adenocarcinomas and mesonephric-like adenocarcinomas in the gynecologic tract: A multi-institutional study. Am J Surg Pathol 2021;45:498–506.
7. Koh HH, Park E, Kim HS. Mesonephric-like adenocarcinoma of the ovary: Clinicopathological and molecular characteristics. Diagnostics (Basel)

2022;12:326.
8. Chen Q, Shen Y, Xie C. Mesonephric-like adenocarcinoma of the ovary: A case report and a review of the literature. Medicine (Baltimore) 2020;99:e23450.
9. Chang CS, Carney ME, Killeen JL. Two cases of mesonephric-like carcinoma arising from endometriosis: Case report and review of the literature. Int J Gynecol Pathol 2023;42:101-7.
10. Dundr P, Gregová M, Němejcová K, Bártů M, Hájková N, Hojný J, et al. Ovarian mesonephric-like adenocarcinoma arising in serous borderline tumor: A case report with complex morphological and molecular analysis. Diagn Pathol 2020;15:91.

Thai Journal of Obstetrics and Gynaecology
July 2024, Vol. 32, No. 4, pp. 320-327.

## CASE REPORT

# Twin Pregnancy Presenting with Hydatidiform Mole and Co-existing Living Fetus with Ovarian Venous Thrombosis: A case report

Karit Jayasakoon, M.D.*,
Densak Pongrojpaw, M.D.*,
Awassada Punyashthira, M.D.*,
Araya Sammor, M.D.**,
Athita Chanthasenanont, M.D.*,
Komsun Suwannarurk, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand*
*** Department of Pathology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand*

### ABSTRACT

**Background:** This case was a twin pregnancy with a complete hydatidiform mole (CHM) and a co-existing fetus. Gestational trophoblastic neoplasia (GTN) and ovarian venous thrombosis (OVT) were diagnosed during the postpartum period.

**Case:** A 25-year-old pregnant woman, gravid 2, para1-0-0-1 presented with vaginal bleeding. Ultrasonography showed multi-cystic placenta separated from a normal placenta and a living fetus. The patient had a vaginal delivery at $31^{+5}$ weeks of gestation. Placental histology described a CHM and negative p57(kip2) immunohistochemistry. Post-molar GTN was diagnosed after one month of delivery. Low-risk GTN was diagnosed with OVT. Clinical symptoms subsided after administrating of single-agent methotrexate and an anticoagulant and without complication during one year follow-up.

**Conclusion:** CHM with a co-existing fetus needs imaging, prenatal genetics, and pathological plus p57(kip2) immunohistochemistry for diagnosis.

**Keywords:** molar pregnancy, trophoblastic disease, co-existing normal fetus, venous occlusion.

***Correspondence to:*** *Densak Pongrojpaw, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand. E-mail: pongrojpaw@gmail.com*

**Received:** 30 September 2023, **Revised:** 3 December 2023, **Accepted:** 16 January 2024

# *ตั้งครรภ์แฝดร่วมกับครรภ์ไข่ปลาอุกและมีภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่หลังคลอด, รายงานผู้ป่วย 1 ราย*

***คริษฐ์ จายะสกุล, เด่นศักดิ์ พงศ์โรจน์เผ่า, อวัสดา บุณยัษเฐียร, อารยา สามหมอ, อธิตา จันทเสนานนท์, คมสันติ์ สุวรรณฤกษ์***

***บทคัดย่อ***

ผู้หญิงตั้งครรภ์อายุ 25 ปี ตั้งครรภ์ครั้งที่ 2 มาโรงพยาบาลด้วยเรื่องเลือดออกผิดปกติจากช่องคลอด ตรวจด้วยคลื่นเสียงความถี่สูงพบครรภ์แฝดของทารกที่มีชีวิตและพบลักษณะถุงน้ำปริมาณมากในมดลูกซึ่งแยกออกจากรก ผู้ป่วยคลอดทางช่องคลอดก่อนกำหนดที่อายุครรภ์ 31 สัปดาห์ 5 วัน ผลพยาธิวิทยาของรกวินิจฉัยครรภ์ไข่ปลาอุกและส่งตรวจทางอิมมูโนฮีสโตเคมี P57 ผลเป็นลบ ผู้ป่วยได้รับติดตามหลังคลอด 1 เดือนตรวจพบมะเร็งเนื้อรกที่มีความเสี่ยงต่ำหลังตั้งครรภ์ไข่ปลาอุกและพบภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่ ได้รับการรักษาด้วยยาเคมีบำบัดชนิดเดี่ยวเมโธเทรกเซตและยาละลายลิ่มเลือด โดยผู้ป่วยได้รับการติดตาม 1 ปี ไม่พบภาวะแทรกซ้อน

การตั้งครรภ์แฝดร่วมกับครรภ์ไข่ปลาอุกมีโอกาสคลอดครรภ์แฝดที่มีชีวิตพบได้ร้อยละ 50 โดยอัตราส่วน 2 ใน 3 คลอดก่อนกำหนด และมีความเสี่ยงต่อภาวะแทรกซ้อนของมารดาและทารก และความเสี่ยงต่อมะเร็งเนื้อรกมากกว่าการตั้งครรภ์ไข่ปลาอุกเดี่ยว ซึ่งผู้ป่วยควรได้รับคำแนะนำแนวทางการรักษาและความเสี่ยง ภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่ในรายที่ไม่มีอาการยังไม่มีการรักษาที่เป็นมาตรฐาน โดยยังเป็นที่อภิปรายระหว่างการให้ยาละลายลิ่มเลือดร่วมกับยาฆ่าเชื้อ การให้ยาละลายลิ่มเลือดอย่างเดียวหรือไม่ได้รับยา

***คำสำคัญ**: ครรภ์ไข่ปลาอุก, ครรภ์แฝดร่วมกับครรภ์ไข่ปลาอุก, ภาวะลิ่มเลือดอุดตันเส้นเลือดดำ*

## Introduction

Gestational trophoblastic disease is a spectrum of related diseases originating from abnormal placenta trophoblast proliferation. Pathogenesis arises from abnormal chromosome fertilization between ovum and sperm. The incidence of co-existing twins with complete molar pregnancy is 1:22,000–100,000 pregnancies[1]. Co-existing twin with complete molar pregnancy refers to one chromosomally normal fetus paired with diploid molar pregnancy. Presentation of co-existing twins with complete molar pregnancy includes antepartum bleeding, hyperemesis gravidarum, thyrotoxicosis[2]. If multiple cystic placentae with viable fetus were detected during antenatal ultrasound, the differential diagnosed include co-existing twin with complete molar pregnancy, partial hydatidiform mole or placenta mesenchymal disease. Co-existing twins with complete molar pregnancy increases the rate of medical complications, for instance antepartum hemorrhage, pregnancy induced hypertension, thyrotoxicosis, and preterm delivery[3]. Major congenital anomalies have not been reported[4]. Termination or expectant management is controversial. Intrapartum, vaginal delivery or caesarean section are definitely not delivery route determination. The risk for gestational trophoblastic neoplasia (GTN) increases when compared between co-existing molar with normal pregnancy and singleton molar pregnancy[5]. Postpartum surveillance should monitor beta human chorionic gonadotropin (β-hCG) to detect post molar gestational trophoblastic neoplasia. Contraception is preferable during the monitoring period to prevent confusion in rising β-hCG[4].

The present study reported a structurally normal female fetus co-existing with the abnormal vesicular placenta. The pathology reported complete hydatidiform mole. Nevertheless, the probability of viable fetal outcomes and post-molar GTN rate remains debated. We reviewed previous literature according to this case.

## Case report

The patient was a 25-year-old Thai pregnant female, gravida 2, para 1-0-0-1, twenty fourth weeks plus four days of gestational age by last menstrual period confirmed by ultrasound at $16^{+2}$ weeks. She presented with one-time abnormal uterine bleeding 4 weeks prior to primary hospitalization. Then, she was referred to Maternal Fetal Medicine unit at Thammasat University Hospital. She denied abdominal pain, water broken nor passing tissue. Speculum examination showed minimal bloody discharge and closed cervix. Her pregnancy resulted from natural conception. She denied abnormal past medical nor surgical history. Primary gravida was delivered via vaginal route 4 years ago. The vital signs were normal. The uterus size was 25 centimeters from pubic symphysis. Other findings were within normal limits. The transabdominal ultrasound finding showed a single alive fetus. Fetal anomaly scan was normal. Multiple cystic placentae with normal placenta were detected (Fig. 1) and color doppler flow was performed (Fig. 2). Corpus luteal cyst was not identified. Laboratory investigations were sent. Serum for β-hCG was 195,814 mIU/ml, more than the upper limit of comparable gestational age. The thyroid function test was in range (thyroid stimulation hormone was 1.06 uIU/mL, Thyroxine was 2.54 ng/dL). Amniocentesis was performed. Quantitative fluorescence polymerase chain reaction (QF-PCR) showed diploidy (XX), aneuploidy chromosome 13,18,21 was not detected.

The patient was counseled regarding the possible risk of pregnancy, fetus, and complications and pregnancy was continued. Antepartum care, fetal growth and wellbeing were monitored. Blood pressure was within normal limits. Blood for β-hCG was collected weekly (Fig. 3). The newborn had preterm vaginal delivery at $31^{+5}$ weeks of gestational age. Her intrapartum blood loss was 1,000 ml from incomplete placental delivery. Suction and curettage were performed. Microscopic description showed a few enlarged villi with focal central cistern and marked trophoblastic proliferation (Fig. 4). Immunohistochemistry p57(kip2) was negative in villous cytotrophoblast and villous stroma. At postpartum serum β-hCG were 598, 240, 608, 1,566 mIU/mL in the follow-up weekly blood sampling. Therefore, post molar gestation trophoblastic neoplasia was diagnosed by rising in β-hCG (Fig. 5).

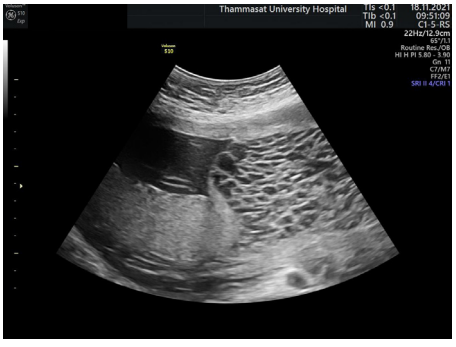


**Fig. 1.** Transabdominal ultrasound shown multiple cystic placentae with normal placenta.

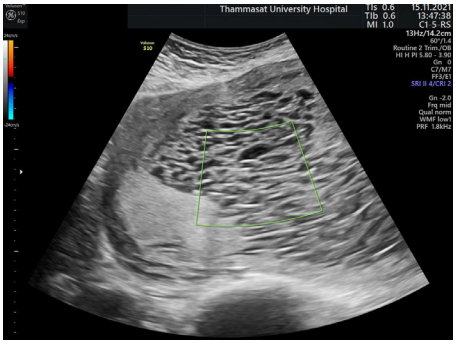


**Fig. 2.** Transabdominal ultrasound shown multiple cystic placentae with absent color doppler flow.

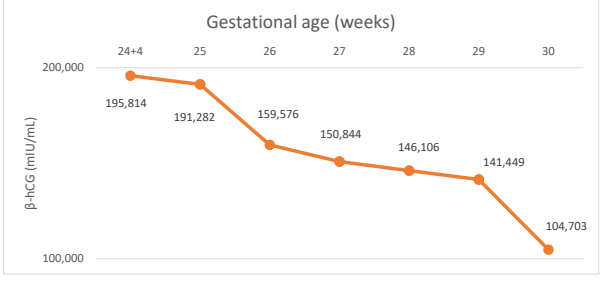


**Fig. 3.** Blood for antepartum B-hCG level.

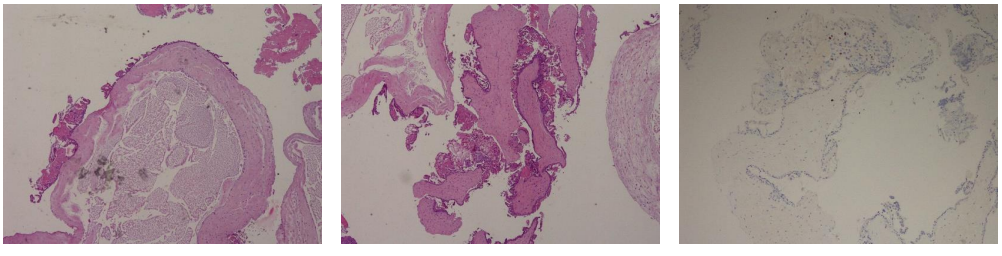

**Fig. 4.** Microscopic description shows a few enlarged villi with focal central cistern and marked trophoblastic proliferation. Immunohistochemistry P57 was negative in villous cytotrophoblast and villous stroma.

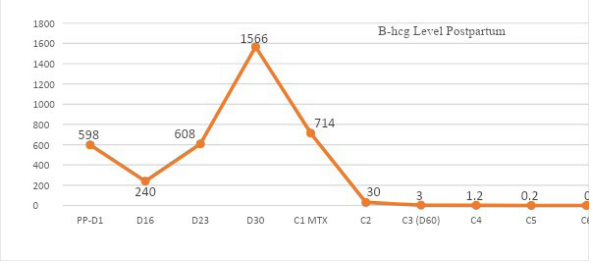


**Fig. 5.** Beta- human chorionic gonadotropin level, PP-D1: postpartum day 1, C1 MTX: 1st cycle of methotrexate.

Computed tomography (CT) showed no distant metastasis. Bilateral ovarian vein thromboses (OVT) were detected. The International Federation of Gynecology and Obstetrics (FIGO) stage was 1. The World Health Organization scoring system, also known as FIGO score, was 3 points. The single-agent chemotherapy (methotrexate) was administered. The β-hCG level declined to normal within three cycles of chemotherapy, and two additional courses were administrated. Low molecular weight heparin (LMWH) was administrated along with chemotherapy. After six months of anticoagulant treatment, an abdominal CT venogram reported decreased size and extension of venous thrombosis at the right ovarian vein. Complete recanalization of the right ovary without clinical symptoms was found. A left ovarian vein and other venous vessels were intact with no filling defect. During one year follow-up, condom was used as a contraceptive method and menstrual cycle was regular interval. The preterm newborn was born with birthweight 1,500 gram with Apgar score 8,10 and stayed at the hospital for 1 month before discharged (Fig. 6).

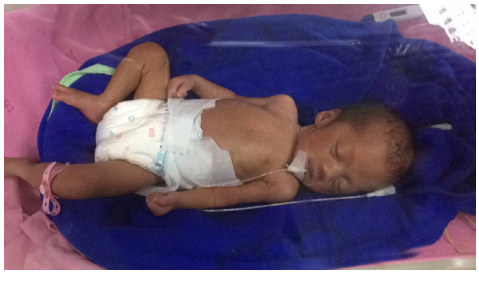

**Fig. 6.** The preterm newborn was born with birthweight 1,500 gram with Apgar score 8,10.

## Discussion

Gestational trophoblastic disease covers both benign and malignancy diseases. Benign conditions include complete hydatidiform mole and partial hydatidiform mole, while GTN, a malignant condition, includes post-molar GTN, invasive mole, choriocarcinoma, placenta site trophoblastic tumor, and epithelioid trophoblastic tumor[4]. Co-existing fetus with complete mole (normal fetus with mole placenta) is a very rare condition. This is the first case of coexisting fetus with complete mole at Thammasat University Hospital.

During prenatal ultrasonography, detecting complex cystic placenta with normal fetus is challenging. The differential diagnoses are co-existing twin with complete mole, partial mole, and placental mesenchymal dysplasia (PMD). Co-existing twins with complete mole may show normal viable fetus. However, both PMD and partial hydatidiform mole may be associated with fetal abnormality, such as fetal growth restriction and Beckwith-Wiedemann syndrome in PMD[6]. McNally reported that blood β–hCG above 200,0000 IU/L was found in coexisting fetus with mole[7].

Histology can be helpful to differentiate hydatidiform mole and PMD. When comparing histology, hydatidiform mole consists of trophoblastic hyperplasia, while trophoblastic dysplasia is not found in PMD[6]. Immunohistochemistry (p57 (kip2)) is used to detect paternal genes, which are positive in partial mole[4]. Meanwhile, trophoblastic proliferation with p57(kip2) negative was reported in cytotrophoblasts and villous stroma. In this subject, co-existing twins with complete molar pregnancy was confirmed.

Some reports had proposed the selective use of other essays, such as fluorescence in situ hybridization (FISH), microsatellite genotype, or single nucleotide polymorphism (SNP) -microarray analysis, to clarify the diagnosis[8]. Fetal karyotype should be performed during prenatal diagnoses such as chorionic villus sampling, maternal cell-free deoxyribonucleic acid (DNA) testing, or amniocentesis

according to gestational age[8, 9].

The previous reports were summarized and presented in Table 1. Morbidity and mortality in current pregnancy included antepartum hemorrhage (60-70%), pregnancy induce hypertension (15.30%), thyrotoxicosis (15-25%), pulmonary edema (10%), and postpartum hemorrhage (10%)[1, 2, 10, 11]. In 2020, Sharon reported eighty percent of twin pregnancies with obstetric complications[2]. In Suksai's review literature, one-third (66/183) subjects required termination of pregnancy due to maternal complications[11]. Thus, maternal complications must be advised. The choice of management between continuation of pregnancy and termination of pregnancy would be determined. In Irani's study, there was no subject with term delivery (0/14), while 5/14 subjects had preterm delivery. Lin et al in 2017 reported 72 coexisting twins with molar pregnant woman; ten of which chose elective termination, while 60 decided to continue with pregnancy. During follow-up antenatal care among conservative pregnancies, the subjects had delivered 25 preterm and 11 term newborns. Twelve (7/60) percent ended the pregnancy with termination due to maternal complication. Lin suggested that the risk for developing subsequent post molar GTN was not significant between subjects who chose continued pregnancy and elective termination.

**Table 1.** Clinical presentation.

| | **Sharon NZ, 2020** | **Lin LH, 2017** | **Irani RA, 2021** | **Present Study** |
|---|---|---|---|---|
| Literature | Systematic | Retrospective | Review | Case |
| number of cases | 244 | 72 | 14 | 1 |
| Incidence | 1/22,000-100,000 | | | NA |
| Diagnosis GA* | 12-23 | 15 (9-30) | 12 (9-19) | 24 |
| Median B-hcg | NA | 400,000 | 355,494 | 195,814 |
| Abortion vs Pregnancy (%) | 25.4 vs 74.6 | 13.9 vs 83.3 | 21.0 vs 63.3 | Pregnancy |
| Obstetrics complication (%) | | | | |
| Vaginal bleeding | 70.5 | 59.0 | 71.0 | Yes |
| Preeclampsia | 14.3 | 32.0 | 28.9 | No |
| Hyperthyroid | 23.5 | 14.0 | 0.7 | No |
| RDS | NA | 9.7 | 0.7 | No |
| Fetal viability | 50.0 | 60.0 | 55.6 | Yes |
| Preterm | 78.0 | 69.0 | 100.0 | 31 weeks |
| IUFD | 40.1 | 28.0 | NA | No |
| Overall complications | 80.8 | 63.0 | NA | No |
| Post-molar GTN (%) | 34.0 | 46.0 | 28.6 | GTN |

* mean (range) weeks
GA: gestational age, β-hcg: beta- human chorionic gonadotropin, RDS: respiratory distress syndromes such as pulmonary embolism or pulmonary edema, IUFD: intrauterine fetal death, GTN: gestational trophoblastic neoplasia, NA: not available

In most cases delivery via cesarean route due to preeclampsia with a severe feature, hemolysis, suspected invasive moles and abnormal fetal presentation[5, 7, 10, 12]. The presenting case delivered by vaginal delivery without severe complications. Postpartum surveillance should monitor β-hCG the

same as hydatidiform mole[4]. Diagram for management is shown in Fig. 7. The route of delivery remains controversial. Nonetheless, elective caesarean section is not recommended.

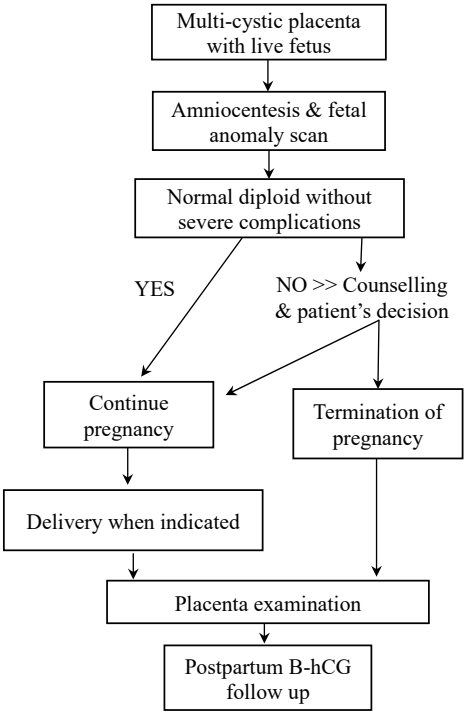


**Fig. 7.** Diagram for management multi-cystic placenta with a live fetus[7,10,12].

The risk of postpartum post molar GTN is 28.6-46%[1, 2, 7, 10] which is higher than those of complete and partial mole: 7-30 and 2.5-7.5%, respectively[4]. Blood for β–hCG should be monitored. Oral contraception is recommended to suppress endogenous luteinizing hormone (LH) and follicle stimulating hormone (FSH)[4].

Ovarian venous thrombosis (OVT) is a rare condition. The typical symptoms were abdominal pain, fever, and palpable mass[13]. Imaging modalities for diagnosis were the ultrasound (US), CT, and magnetic resonance imaging (MRI). In a systematic review, the sensitivity and specificity for the diagnosis by the US were 50-100% and 41-99%, respectively. Sensitivity and specificity of CT were 70-100% and 62-99%, respectively. The best investigation was MRI, with nearly 100% sensitivity and specificity[13]. This study incidentally identified bilateral OVT from a metastatic workup without clinical symptoms. The ovarian thrombus can extend to major vessels such as inferior vena cava (15%), renal vein (12%), and pulmonary vein (10%)[14, 15]. Riva et al reported risk factors of OVT were malignancy, postpartum, oral contraceptive pills, pelvic surgery, and pelvic infection. Treatment of OVT is controversial. There are three options from the previous literature. First, a combination of antibiotics and anticoagulants was administered. The board-spectrum antibiotics should be medicated until the fever resolved at least 48 hours. Anticoagulant was administered for 1 to 3 months, according to the Canadian Society of Obstetrics and Gynecologists 2014[16]. Second, only anticoagulant was administered for 3 to 6 months according to the guidelines of the British Committee for Standards in Hematology 2012[17]. Third, no treatment in asymptomatic incidentally detected isolated OVT in a patient with malignancy[17]. The extent of anticoagulation duration varies between 3 to 6 months with LMWH, oral

anticoagulant, or vitamin K antagonist[13]. OVT in post-molar GTN is rare condition, only one case report was evident by KIM et al,[18] In this study, an incidental OVT was diagnosed along with post-molar GTN. LMWH administered the treatment for 6 months. The clinical subsided without complications such as premature ovarian failure, renal failure and pulmonary embolism.

## Acknowledgments

We want to thank participant and the staff at Thammasat Hospital. Especially Pimkul Luamprapat and Supisara Mungkornthongsakul for case and literature review.

## Potential conflicts of interest

The authors declare no conflicts of interest.

### References

1. Lin LH, Maestá I, Braga A, Sun SY, Fushida K, Francisco RPV, et al. Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: A retrospective multicenter cohort and literature review. Gynecol Oncol 2017;145:88-95.
2. Sharon NZ, Maymon R, Melcer Y, Jauniaux E. Obstetric outcomes of twin pregnancies presenting with a complete hydatidiform mole and coexistent normal fetus: a systematic review and meta-analysis. BJOG 2020;127:1450-7.
3. Cunningham FG, Leveno KJ, Dashe JS, Hoffman BL, Spong CY, Casey BM. Gestational trophoblastic disease. Williams obstetrics. 26th ed. New York; McGraw-Hill Education 2022:235-44.
4. Soper JT. Gestational trophoblastic disease: Current evaluation and management. Obstet Gynecol 2021;137:355-70.
5. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet 2021;155:86-93.
6. Colpaert RM, Ramseyer AM, Luu T, Quick CM, Frye LT, Magann EF. Diagnosis and management of placental mesenchymal disease. A review of the literature. Obstet Gynecol Surv 2019;74:611-22.
7. McNally L, Rabban JT, Poder L, Chetty S, Ueda S, Chen LM. Differentiating complete hydatidiform mole and coexistent fetus and placental mesenchymal dysplasia: A series of 9 cases and review of the literature. Gynecol Oncol Rep 2021;37:100811.
8. Lin M, Chen J, Liao B, He Z, Lin S, Luo Y. When a vesicular placenta meets a live fetus: case report of twin pregnancy with a partial hydatidiform mole. BMC Pregnancy Childbirth 2021;21:694.
9. Gabra MG, Gonzalez MG, Bullock HN, Hill MG. Cell-free DNA as an addition to ultrasound for screening of a complete hydatidiform mole and coexisting normal fetus pregnancy: a case report. Am J Perinatol Rep 2020;10:e176–8.
10. Irani RA, Holliman K, Debbink M, Day L, Mehlhaff K, Gill L, et al. Complete Molar pregnancies with a coexisting fetus: Pregnancy outcomes and review of literature. AJP Rep 2021;12:e96-e107.
11. Suksai M, Suwanrath C, Kor-Anantakul O, Geater A, Hanprasertpong T, Atjimakul T, et al. Complete hydatidiform mole with co-existing fetus: Predictors of live birth. Eur J Obstet Gynecol Reprod Biol 2017;212: 1-8.
12. Lipi LB, Philp L, Goodman AK. A challenging case of twin pregnancy with complete hydatidiform mole and co-existing normal live fetus - A case report and review of the literature. Gynecol Oncol Rep 2019;31:100519.
13. Riva N, Calleja-Agius J. Ovarian vein thrombosis: A narrative review. Hamostaseologie 2021;41:257-66.
14. Labropoulos N, Malgor RD, Comito M, Gasparis AP, Pappas PJ, Tassiopoulos AK. The natural history and treatment outcomes of symptomatic ovarian vein thrombosis. J Vasc Surg Venous Lymphat Disord 2015;3:42–7.
15. Gakhal MS, Levy HM, Spina M, Wrigley C. Ovarian vein thrombosis: analysis of patient age, etiology, and side of involvement. Del Med J 2013;85:45–50.
16. Chan WS, Kent NE, Rey E, Corbett T, David M, Douglaset MJ, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can 2014;36:527-53.
17. Tait C, Baglin T, Watson H, Laffan M, Makris M, Perry D, et al. British committee for standards in haematology. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol 2012;159:28–38
18. Kim IY, Kim SH, Hwang IT, Ha JG, Cha JH. A rare case of ovarian vein thrombosis in a gestational trophoblastic neoplasia patient. Obstet Gynecol Sci 2019;62:190-3.