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EDITORIAL

This fifth issue of Thai Journal of Obstetrics and Gynaecology (TJOG) 2023 contains many interesting articles. One special article is "Bacterial vaginosis: A comprehensive approach to management in reproductive-aged Thai women".

The Royal Thai College of Obstetricians and Gynaecologists (RTCOG) Annual Meeting 2023 will be held during 24-27 October 2023 at Dusit Thani Pattaya Hotel, Chonburi, Thailand. The theme of this meeting is "Smart O&G". This meeting will have the Asia & Oceania Federation of Obstetrics & Gynaecology (AOFOG) session on the topic "Violence against women: Roles of ObGyn in the hidden epidemic". All RTCOG members are cordially invited to participate this scientific meeting.

Residents who would like to publish their researches in TJOG should submit their works before September 30, 2023. Our editorial team and constructive reviewers will let them know the results before December 31, 2023.

Wish to see you at RTCOG Annual Meeting 2023 at Dusit Thani Pattaya Hotel, Chonburi, Thailand

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

Thai Journal of Obstetrics and Gynaecology
September 2023, Vol. 31, No. 5, pp. 318-325.

SPECIAL ARTICLE

Bacterial Vaginosis: A Comprehensive Approach to Management in Reproductive-Aged Thai Women

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ABSTRACT

Bacterial vaginosis (BV) is the predominant condition of vaginal dysbiosis leading women to seek gynecologic care. Excessive genital cleansing, particularly through vaginal douching, appears to be a precipitating factor. BV does not induce any inflammatory response, with more than half of patients remaining asymptomatic. The chief complaints are an increased vaginal discharge volume and an altered odor. BV compromises the body's natural defense mechanisms, thereby increasing susceptibility to local and ascending infections. BV also heightens the risk of sexually transmitted infections, including pelvic inflammatory disease. For many years before 2022, our institution employed a metronidazole regimen of 1,200 mg daily, which demonstrated favorable efficacy. Metronidazole commonly leads to side effects such as nausea, vomiting, and a metallic taste. Unfortunately, many women discontinue the medication once their symptoms alleviate, as they often perceive BV as a vaginal imbalance rather than an infectious disease. In 2022, the Royal Thai College of Obstetricians and Gynaecologists introduced a recommended treatment guideline for BV that emphasized a balanced approach to medications and lifestyle modifications. Consequently, the primary antibiotic now used in Thailand is metronidazole, administered as a single 2 g dose or 800 mg daily for 7 days. At the Siriraj Female Sexually Transmitted Infections Clinic, we have utilized various metronidazole treatment regimens accompanied by comprehensive educational sessions and counseling. This article shows a comprehensive approach to management of BV in reproductive-aged Thai women, particularly based on Siriraj experience.

Keywords: bacterial vaginosis, Siriraj experience, treatment, vaginal dysbiosis, metronidazole.

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Introduction

Disruption of the vaginal ecosystem leads to abnormal proliferation of the vaginal flora, characterized by an altered microbial ratio[1]. Bacterial vaginosis (BV) represents the predominant manifestation of vaginal dysbiosis, prompting women to seek gynecologic care[2]. BV arises from an overgrowth of anaerobic bacteria, notably *Gardnerella vaginalis*, resulting in an abundance of vaginal discharge with an unpleasant odor, commonly described as fishy. Notably, BV is not classified as a sexually transmitted infection (STI). Symptoms are often more pronounced during and after menstruation or sexual intercourse, with some individuals experiencing persistent and severe symptoms throughout the day. Nevertheless, nearly half of BV cases are asymptomatic. Dysbiosis weakens the vaginal environment and enhances vulnerability to various infections[3]. BV poses additional concerns in pregnant women, as it may heighten the risks of preterm labor or premature rupture of membranes[4].

The vagina serves as an elastic and muscular canal that links the external genitalia to the cervix. In prepubescent females, the predominant bacteria in the vagina are *E. coli*, diphtheroids, and coagulase-negative *Staphylococcus*[5]. Upon entering reproductive age, increased estrogen levels lead to the proliferation of mature squamous cells and enhanced glycogen accumulation within vaginal epithelial cells. Vaginal enzymes, such as alpha-amylase, degrade glycogen into maltose, maltotriose, and alpha-dextrins. Subsequently, *Lactobacilli's* lactase dehydrogenase hydrolyzes these compounds into lactic acid, which inhibits the growth of other bacteria. Lactic acid is believed to enter the cytoplasm and induce bacterial cell death. *Lactobacilli*, the primary protective bacteria in the vaginal ecosystem, produce both L- and D-lactic acid. However, D-lactic acid specifically contributes to maintaining vaginal balance[6]. Additionally, certain strains of *Lactobacilli*, notably *L. crispatus*, exhibit a higher capacity for hydrogen peroxide production, while *L. iners* produces comparatively low levels of hydrogen peroxide[7].

Both intrinsic and extrinsic factors can easily disrupt the stability of the vaginal ecosystem. Intrinsic factors encompass sex hormone levels and the presence of menstrual blood. Conditions that lead to decreased estrogen levels, such as menopause and breastfeeding, result in reduced quantities of *Lactobacilli* in the vagina. Additionally, the alkalinity of menstrual blood diminishes the activity of lactic acid, creating an environment conducive to the proliferation of other bacteria, thereby disrupting the protective role of *Lactobacilli*. Notably, *L. crispatus*, a beneficial strain of *Lactobacilli*, experiences a significant 100-fold decrease during menstruation, whereas *L. iners* and other anaerobic bacteria exhibit increased abundance[8]. Extrinsic factors encompass birth control methods that cause abnormal bleeding patterns, which can interfere with *Lactobacillus* function like the interaction of menstrual blood. Furthermore, certain risk behaviors, such as vaginal douching, excessive genital cleansing, and intercourse, directly reduce *Lactobacilli* in the vaginal ecosystem.

The Nugent scoring system is considered the gold standard diagnostic method for BV[9]. However, due to the expertise required by examiners, clinical diagnosis methods such as Amsel's criteria have gained popularity. The criteria necessitate the presence of at least three out of four indicators. They are a thin grayish-white homogenous discharge, pH > 4.5, clue cells (vaginal squamous epithelial cells with adherent bacteria), and a positive whiff test (characterized by a fishy odor upon adding 10% KOH)[10]. Nonetheless, a limitation of this method is its inability to be used in cases involving blood or amniotic fluid contamination. To address the limitation, the Royal Thai College of Obstetricians

and Gynaecologists recommends utilizing clue cells as a standalone diagnostic tool for BV, focusing on determining the proportion of clue cells present. An inclusion threshold of at least 20% clue cells achieves a sensitivity and a specificity of 87.1% and 55.8%, respectively, for diagnosing BV[11].

In line with the guidelines provided by the Center for Disease Control and Prevention, the International Union against Sexually Transmitted Infections and the World Health Organization[12, 13], the Royal Thai College of Obstetricians and Gynaecologists has issued treatment recommendations for reproductive-aged women presenting with abnormal vaginal discharge based on the available medications in Thailand[14]. The recommended regimens for BV treatment are follows:

- Metronidazole: 400 - 500 mg orally, twice a day for 7 days,
- Metronidazole: 2 g orally as a single dose,
- Metronidazole: 750 mg vaginal suppositories for 7 days,
- Tinidazole: 2 g orally as a single dose, or
- Clindamycin: 300 mg orally, twice a day for 7 days

Medical personnel should inquire about patients' experiences and comfort with vaginal suppositories, as they may not be suitable for individuals who have never engaged in penetrative sexual intercourse. Premature discontinuation of the regimen is a common issue[15], resulting in the improper disposal of residual drugs into the environment. Therefore, the single-dose regimen is often favored as the initial choice. However, being cautious of potential immediate vomiting following drug intake is crucial. One suggested approach is to slowly consume tablets, ingesting one or two at a time but ensuring that all tablets are swallowed within 5 minutes. As importantly, alcohol-containing food or drink should be withheld until 24 hours following last metronidazole tablet/ suppository or 72 hours until last tinidazole tablet.

It is crucial to ensure that all patients have a comprehensive understanding of the nature of the disease, its underlying causes, appropriate treatment, and self-care measures to prevent recurrence. The key messages to convey are as follows: "BV is not a sexually transmitted disease but rather a disruption in the vaginal ecosystem," "Recurrence is very common if lifestyle modifications are not followed", and "BV can result in many severe diseases, particularly ascending infections." Additionally, it is essential to provide clear explanations regarding proper drug administration and potential side effects. These explanations can be delivered through individualized one-on-one counseling sessions or online platforms. At the Siriraj Female Sexually Transmitted Infections (STI) Clinic, easily comprehensible educational materials have been developed to aid patients in understanding the correct technique for suppository administration and optimal vaginal care (see Fig. 1).

1A) Proper vaginal suppository method

1B) Vaginal care

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University

Fig. 1. QR code for accessing information on the proper usage of vaginal suppositories and vaginal care

Advice regarding proper vaginal care can vary across countries, and no universally agreed-upon best method exists. However, it is generally acknowledged that vaginal douching can lead to complications[16]. In Thailand, 4.8% of asymptomatic reproductive-aged[17] women practice vaginal douching, and this prevalence doubles among those with BV[18]. Surveys indicate that up to 90% of Thai women engage in genital cleansing outside of shower time, with three-thirds doing so at least twice daily[17]. It is important to dispel common myths surrounding vaginal care, such as the belief that urine is unclean, the misconception that a woman's genitals should have no odor, and the notion that seminal fluid must be completely washed out after intercourse. Most Thai women rely on plain water for external genital cleansing[17], whereas women from other countries often prefer various cleansing products[19]. However, once abnormal vaginal discharge is experienced, it is advisable to reduce the habit of internal and external genital cleansing.

The Siriraj Female STI Clinic provides specific recommendations for genital care. First, gentle blotting with dry tissue paper should be performed after urination. Second, sanitary pads should not be used outside of the menstrual cycle. Third, direct spraying of water onto the genitals should be avoided. Fourth, in cases of vaginitis or abnormal vaginal discharge, activities involving water immersion, such as swimming, should be avoided. Finally, if currently engaging in vaginal douching, it is advised to discontinue this behavior.

Experience of treating women with BV at the Siriraj Female STI Clinic

The primary treatment approach for BV involves the use of simple antibiotics, such as metronidazole, in either the oral or vaginal form. Since 2020, the Clinic has implemented a treatment and response monitoring system for all BV patients. Specifically, patients were requested to return for a follow-up visit after 2 weeks. In cases where no treatment response was observed, an alternative regimen was prescribed, with a further follow-up appointment scheduled for the following 2 weeks.

Patient characteristics are detailed in Table 1. Data analysis revealed therapeutic efficacy rates ranging from 66.7% to 80% for all metronidazole regimens (Fig. 2). These findings align with previous studies conducted among Thai women, which reported cure rates ranging from 77.8% to 78.6% based on the Amsel criteria[18, 20]. It should be noted that a proportion of patients, approximately 10%, exhibited two Amsel criteria, indicating an abnormal condition or mild BV[21].

BV often involves the formation of anaerobic biofilms that exhibit poor response to treatment. One study demonstrated that using metronidazole vaginal suppositories is more effective and faster at destroying biofilms[22]. However, our findings indicate that the treatment efficacy of vaginal metronidazole suppositories in combination with miconazole did not differ from that of oral metronidazole[18].

Lactic acid, a weak acid produced by *Lactobacilli*, plays a role in maintaining vaginal balance and acts as a precursor for hydrogen peroxide formation[7]. While lactic acid has been utilized in BV treatment, its efficacy is inferior to that of metronidazole[23, 24]. Therefore, its use is recommended in cases with mild symptoms or when less than three Amsel criteria are met. It is more favorably utilized in combination with metronidazole. Additionally, lactic acid can serve as a long-term preventive measure against BV recurrence and is considered safe for pregnant women[21, 25].

Our observations indicated that lactic acid was well-tolerated by patients. Only 13.6% (3/22) of patients reported a mild burning sensation from the first day of use. One patient also noted a slightly bothersome vaginal discharge, which resolved by the end of the 7-day treatment period. Patients expressed increased satisfaction during

the second and third days of use, reporting improved comfort and reduced odor. However, the treatment efficacy results at the 2-week follow-up did not differ from those of the other groups.

Table 1. Patient characteristics and treatment outcomes by treatment regimen.

	Metronidazole 400mg BID, 7d (n = 33)	Metronidazole 400mg TID, 7d (n = 30)	Metronidazole 2g (n=31)	Metronidazole 2g + Lactic acid (n=22)	Dequalinium chloride (n=22)
Age (years)	32.4±10.1	33.4±10.3	32.6±7.5	33.1±10.8	31.3±10.1
Being parous	12 (36.4)	13 (43.3)	11 (35.5)	8 (36.4)	5 (22.7)
Being pregnant	8 (24.2)	2 (6.7)	2 (6.5)	3 (13.6)	4 (18.2)
Vaginal care					
Panty-liner outside period	18 (54.6)	17 (56.7)	18 (58.1)	13 (59.1)	14 (63.6)
Special genital soap	18 (54.6)	17 (56.7)	15 (48.4)	15 (68.2)	13 (59.1)
Douche	10 (30.3)	5 (16.7)	6 (19.4)	11 (50.0)	6 (27.3)
Tampon	4 (12.1)	0	1 (3.2)	3 (13.6)	3 (13.6)
History of STDs					
Genital warts	5 (15.2)	2 (6.7)	2 (6.5)	1 (4.6)	3 (13.6)
Gonorrhea	2 (6.1)	1 (3.3)	2 (6.5)	1 (4.6)	1 (4.6)
Herpes genitalis	1 (3.0)	2 (6.7)	1 (3.2)	0	0
Trichomoniasis	1 (3.0)	1 (3.3)	0	0	0
Diagnosis of BV (Amsel criteria)					
pH > 4.5	31 (93.9)	29 (96.7)	28 (90.3)	19 (86.4)	20 (90.9)
Whiff test	25 (75.8)	20 (66.7)	27 (87.1)	19 (86.4)	20 (90.9)
Homogeneous whitish discharge	27 (81.8)	28 (84.8)	26 (83.9)	17 (77.3)	14 (63.6)
Presence of clue cells	31 (93.9)	28 (84.8)	30 (96.8)	22 (100)	21 (95.5)
Percentage of clue cells	50 [30-80]	45 [20-70]	40[30-60]	60[50-80]	60[50-90]
Number of Amsel criteria					
3	13 (39.4)	12 (40.0)	12 (38.7)	10 (45.5)	10 (45.5)
4	20 (60.6)	16 (53.3)	19 (61.3)	12 (54.6)	12 (54.6)
At 2-week follow-up					
No symptom	19 (57.6)	22 (73.3)	23 (74.2)	12 (54.6)	8 (36.4)
pH > 4.5	10 (30.3)	12 (40.0)	10 (32.3)	11 (50.0)	7 (31.8)
Whiff test	3 (9.1)	2 (6.7)	3 (9.7)	4 (18.2)	3 (13.6)
Homogeneous whitish discharge	5 (15.2)	1 (3.3)	5 (16.1)	2 (9.1)	6 (27.2)
Presence of clue cells	12 (36.4)	11 (36.7)	12 (38.7)	9 (40.9)	13 (59.1)
Presence of pseudohyphae	8 (24.2)	9 (30.0)	10 (32.3)	8 (36.4)	2 (9.1)
Presence of cervicitis*	3 (9.1)	4 (12.1)	2 (6.5)	1 (4.6)	2 (9.1)
Recurrence at 2 months	1/18 (5.6)	2/30 (6.7)	2/30 (6.7)	1/5 (20.0)	0/2 (0)

Abbreviation: BV, bacterial vaginosis, *Cervicitis = leukocytes ≥30/high power field (under 400x microscope)

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University

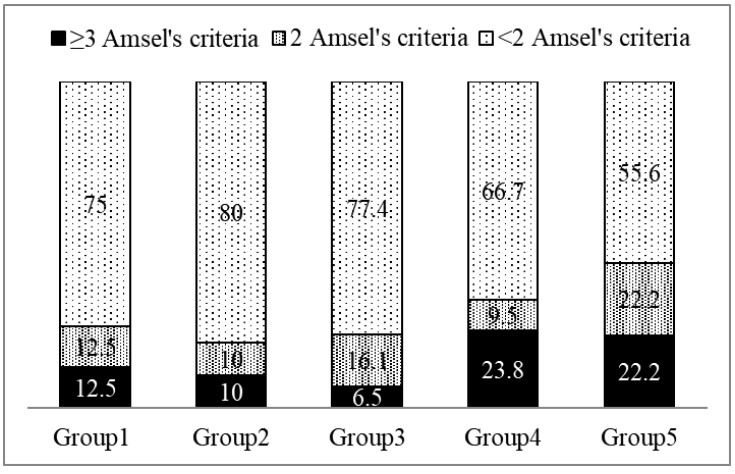

Fig. 2. Cure rates based on Amsel criteria at 2-week follow-up

Group 1 = Metronidazole 400mg BID, 7d (n = 33); Group 2 = Metronidazole 400 mg TID, 7d (n = 30); Group 3 = Metronidazole 2g (n = 31); Group 4 = Metronidazole 2g + Lactic acid (n = 22); Group 5 = Dequalinium chloride (n = 22)

Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University

Dequalinium chloride is an antiseptic agent that can eradicate *G. vaginalis* biofilms[26], making it a potential treatment option for BV. However, our experience revealed an effectiveness rate of only 55.6%, with 22.2% of participants still exhibiting two Amsel criteria. Further studies are required to investigate the use of this drug. Our preliminary findings suggest that dequalinium chloride is an alternative treatment for patients who prefer to avoid antibiotics. Additionally, our previous report showed that its additional benefit was a non-inferior efficacy to clotrimazole in treating women with vaginal candidiasis[11]. As up to 36.4% of women with BV demonstrated vaginal candidiasis at the 2-week follow-up, dequalinium chloride may be advantageous. Nevertheless, close monitoring of treatment response is necessary, as antibiotics or antimycotics may eventually be needed.

Another non-antibiotic therapy for BV is *Lactobacillus* suppository since its deprivation is the mainstay pathophysiology. The only product in the Hospital's drug list is a combination of estriol 0.03 mg and 10^8 CFU of *Lactobacillus acidophilus*. Previous studies showed that, in terms of cure rate, it was superior to placebo and non-inferior to antibiotics[27, 28]. Using the combination as the first line BV treatment, we found that 10/20 (50.0%) women were symptom-free at 2-week follow-up but seven of them met at least three Amsel criteria. Out of the twenty patients, six met four Amsel criteria, seven met three, and five met two criteria at 2-week follow-up. Like dequalinium chloride, this product may be an option for those who prefer non-antibiotic treatment.

Currently, we have limited experience of using tinidazole and clindamycin. Tinidazole is a long-acting nitroimidazole antibiotic but is not included in the Hospital's drug list. Based on the data of 9 non-pregnant women with BV who came for 2-week follow-up, a 7-day-course of twice daily 300mg clindamycin showed lower cure rate by Amsel criteria than that in a previous study in Thailand[29], at 66.7% vs 94.3%. Moreover, we found one case of angioedema following clindamycin consumption.

Regarding symptom assessment, it was observed that the group receiving metronidazole 400 mg three times daily for 7 days displayed the fewest symptoms on the follow-up day (Table 1). However, this group expressed the highest level of dissatisfaction with the treatment approach. The regimen of metronidazole 400 mg three times daily for BV

treatment has been in use at Siriraj Hospital for over 20 years. At the moment, the Clinic maintains this regimen for cases that do not respond to the initial treatment, and it has shown a treatment efficacy rate of nearly 100%. For those who failed the regimen of 7-day metronidazole 1,200 mg, the 12-day course of dequalinium chloride was then prescribed and resulted in good treatment response.

When being assessed at two months, recurrence was rare. Three main causes of BV recurrence were residual infection, resistance to treatment, or re-infection[25]. The first two causes are unlikely since the follow-up until being cured was performed in all cases. This underlines the importance of education session about vaginal health care and follow-up for all women with BV. Nonetheless, longer term follow-up and further studies are required in order to demonstrate the sole effect of lifestyle modification on BV recurrence.

Beside treatment outcomes, the new diagnoses which were disclosed at 2-week follow-up were as important. Up to 36.4% of women initially being diagnosed with BV were positive for pseudohyphae, a marker of vaginal candidiasis, under light microscope. We chose to treat all of them regardless of symptoms and asked them to return for evaluation until the finding became negative. In contrast, although presence of leukocytes ≥ 30/high power field (under 400x magnification) yields diagnostic accuracy of chlamydial cervicitis at 21.8%[30], we did not initiate treatment. Further information is required to guide clinicians' decision.

Conclusion

Vaginal dysbiosis is a challenge for obstetricians and gynecologists because of its potential severe consequences. The main precipitating factor is the patient's genital care practice which needs to be discussed, investigated and modified in conjunction with drug treatment. The choices of treatment regimens are at the moment vast. The prescriptions should be based on to the experience of the healthcare personnel and the acceptance of the patients. This article shows that higher-dose drug use may not improve the patient's recovery rate. Guidelines for treating this group of patients still have room for further development to provide patients with the best possible care.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

A Comparison of the LATCH Scores between Groups of Breastfeeding Women Using and Not Using a Nursing Pillow: A randomized, controlled trial

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ABSTRACT

Objectives: To investigate if the U-shaped nursing pillow can improve the LATCH scores in the postpartum breastfeeding mothers.

Materials and Methods: Postpartum women who had an uncomplicated vaginal delivery and intended to breastfeed were eligible. Mothers who had no contraindications to breastfeeding were randomized into two groups: the nursing-pillow intervention group and the control group. All participants underwent breastfeeding education and training regarding the proper body position. They used a modified cradle technique 2-4 hours postpartum under the guidance of a well-trained breastfeeding nurse. The mothers in the intervention group were instructed to use the U-shaped nursing pillow, size 60 x 60 cm, with 25 - 30 cm thickness during every breastfeeding while they were in the maternity ward. The LATCH scores were assessed at 48 hours postpartum. The primary outcome was a mean difference in the LATCH scores between the groups.

Results: A total of 48 eligible mothers were randomized into two groups: 24 in the nursing-pillow intervention group and 24 in the control group. The LATCH scores of the women who used a nursing pillow were significantly higher. The mean difference was 0.48 (95% confidence interval 0.06-0.90, p = 0.027).

Conclusion: The groups of breastfeeding women using the U-shaped nursing pillow had higher LATCH scores than the control group.

Keywords: nursing pillow, breastfeeding practices, LATCH score.

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การศึกษาเปรียบเทียบคะแนนการเข้าเต้า (LATCH score) ในสตรีให้นมบุตรระหว่างการให้นมบุตรโดยใช้หมอนรองให้นมบุตรกับการให้นมบุตรโดยไม่ใช้หมอนรองให้นมบุตร: การทดลองแบบสุ่มและมีกลุ่มควบคุม

ศุภกิจ ศิริกิจขจร, เมสิตา สุขสมานวงศ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบคะแนนการเข้าเต้า (LATCH score) ในสตรีให้นมบุตรระหว่างการใช้หมอนรองให้นมบุตรกับการให้นมโดยไม่ใช้หมอนรองให้นมบุตร*

วัสดุและวิธีการ: *ทำการศึกษาในกลุ่มสตรีหลังคลอดที่คลอดบุตรทางช่องคลอดที่โรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี และไม่มีภาวะแทรกซ้อนหลังคลอด ซึ่งสตรีที่ตั้งใจเลี้ยงลูกด้วยนมแม่และไม่มีข้อห้ามในการเลี้ยงลูกด้วยนมแม่ จะถูกแบ่งเป็นสองกลุ่มแบบสุ่ม คือ กลุ่มที่ใช้หมอนรองให้นมในการให้นมบุตร และกลุ่มที่ไม่ใช้หมอนรองให้นม โดยสตรีหลังคลอดทุกรายจะได้รับคำแนะนำและช่วยเหลือในการเข้าเต้า รวมถึงการจัดท่าทางในการให้นมอย่างถูกต้อง คะแนนการเข้าเต้าจะถูกประเมินที่ 48 ชั่วโมงหลังคลอด และคะแนนการเข้าเต้าของทั้งสองกลุ่มจะนำมาเปรียบเทียบทางสถิติ*

ผลการศึกษา: *สตรีหลังคลอดจำนวน 48 คน ได้รับการแบ่งกลุ่มแบบสุ่มเป็น 2 กลุ่ม กลุ่มละ 24 คน คือ กลุ่มที่ให้นมโดยใช้หมอนรองให้นมบุตร และกลุ่มที่ไม่ได้ใช้หมอนรองให้นมบุตร พบว่า คะแนนการเข้าเต้าของกลุ่มที่ใช้หมอนรองให้นมบุตรสูงกว่าอย่างมีนัยสำคัญทางสถิติ โดยมีผลต่างของค่าเฉลี่ยของทั้ง 2 กลุ่มเท่ากับ 0.48 (95%Confidence interval 0.06-0.90, p = 0.027).*

สรุป: *คะแนนการเข้าเต้าของกลุ่มที่ใช้หมอนรองให้นมบุตรสูงกว่ากลุ่มที่ไม่ได้ใช้หมอนรองให้นมบุตรอย่างมีนัยสำคัญทางสถิติ*

คำสำคัญ: *หมอนรองให้นมบุตร, คะแนนเข้าเต้า, การเลี้ยงลูกด้วยนมแม่, LATCH score*

Introduction

The World Health Organization (WHO) has encouraged exclusive breastfeeding for at least six months after child delivery[1]. Breastmilk contains enriched nutrients that support growth, cognitive function, and future health throughout one's life[2]. Precise and correct breastfeeding techniques help the mother to continue breastfeeding for at least six months. The LATCH score is one of the best predictors of breastfeeding effectiveness[3]. The score can also predict compliance with adequate exclusive breastfeeding[4-7]. The appropriate breastfeeding techniques allow the mother to feel comfortable and relaxed because the back, feet, and breasts are well-rested. The fetal position matters, as well. The fetus's body should be on a single axis, with head and body support, and the body should contact the mother[8-10].

During breastfeeding, almost women reported deep pain in the lower abdomen, low back, and breasts[11]. The reported lower back pain increased with each breastfeeding duration. The rate of low back pain was lower when lumbar supports were used during nursing. Moreover, the degree of low back pain decreased associated with the thickness of lumbar support[12]. A nursing pillow is one of the tools that may help improve the breastfeeding position. The current study showed a significant reduction in maternal discomfort during breastfeeding time among participants using a nursing pillow[13].

In current practice at the HRH Princess Maha Chakri Sirindhorn Medical Center, all postpartum women have to undergo breastfeeding education and be trained by a well-trained nurse. The mother can use a nursing pillow during breastfeeding if she wants. However, no previous study has shown the benefit of nursing pillows. We aimed to investigate if nursing pillows can improve the LATCH scores in immediate postpartum mothers.

Materials and Methods

This randomized control trial was conducted at the HRH Princess Maha Chakri Sirindhorn Medical Center in Nakhon Nayok province, Thailand. The study period lasted from June to September 2021. The study had been approved by The Ethics committee of the Srinakharinwirot University, Faculty of Medicine, and registered at the Thai Clinical Trials Registry (registration number TCTR20220317001). The eligible population was all postpartum women who underwent an uncomplicated vaginal delivery and intended to breastfeed. The neonates had to weigh more than 2,500 grams at birth and had no birth complications or defects that could affect breastfeeding, such as cleft lip and palate, respiratory distress, or severe tongue tie. Also, the participants had to have no contraindications to breastfeeding. Informed consent was obtained from all participants. Postpartum women who refused to participate in the research, along with mothers who have breast or nipple problems, and whose infants were diagnosed with galactosemia, were excluded.

The sample size was calculated based on 0.05 of α error, 0.8 of power, a mean difference of 0.8, and a standard deviation of 0.9. Twenty percent dropped-out had been added. The total number of people in each group was 24.

The position of breastfeeding is one of the major confounding factors. The modified cradle technique is the simplified breastfeeding positions in which the mother uses one hand to hold the breast and the other to support the baby's head. This position is easy for beginners. All participants received breastfeeding education and proper body positioning in a modified cradle technique for 30 minutes at 2 - 4 hours postpartum under the guidance of a well-trained nurse. Breastfeeding was encouraged every 2 - 3 hours during the admission period.

All participants were randomized into two groups. The first group breastfed using the U-shaped nursing pillow, size 60 x 60 cm, with 25 - 30 cm thickness every time they breastfed their babies during hospital admission to help the mothers avoid bending their back during breastfeeding. The pillow is made of cotton or synthetic fiber which can support the weight well. This U-shape nursing pillow is accessible at local stores. The control group breastfed without a

U-shape nursing pillow. However, there was the possibility of using other kinds of pillows during admission. The participants in both groups were helped to breastfeed in a comfortable, modified cradle position by a well-trained nurse. The quality of the breastfeeding was evaluated at 48 hours postpartum using LATCH scores that included a latch, audible, a type of nipple, a comforting breast, and nipple hold as described in Table 1[14]. The scores were measured by two well-trained nurses. Neither of them knew the score given by the other. Concerning not being able to blind the intervention, bias was therefore reduced by retraining evaluators to set control standards for assessment results. The assessment has been revised and retested many times to control assessment results to the same standard before the beginning of the study. We assessed the LATCH score 48 hours postpartum because there is evidence that the LATCH score 48 hours after birth can predict the rate of exclusive breastfeeding at 6 weeks postpartum[4-6] and identified mothers who need breastfeeding support before discharge from the hospital to prevent early breastfeeding cessation. The flow diagram of participants throughout the study is shown in Fig. 1.

The secondary outcome was a fatigue level assessed by a visual analog scale which was assessed simultaneously with the LATCH scores.

The demographic data presented as mean and standard deviation, median and interquartile range or number and percentage. We used the intention-to-treat analysis method. A p value < 0.05 was considered statistically significant. We used the t-test to compare the LATCH score, and the fatigue level of those who used and did not use a nursing pillow. The statistical analysis was performed using SPSS software (version 23.0; SPSS Incorporated).

Table 1. LATCH scores[14]

LATCH score		Detailed
L = Latch	2	Grasps breast, tongue down and forward Lips flanged and has rhythmic suckling
	1	Repeated attempts Holds nipple in mouth Stimulated to suck
	0	Too sleepy or reluctant No latch obtained
A = Audible swallowing	2	Spontaneous or frequent audible swallowing
	1	A bit of audible swallowing with stimulation
	0	None
T = Type of nipple	2	Everted (after stimulation)
	1	Flat
	0	Inverted
C = Comfort	2	Soft, non-tender, intact nipple
	1	Filling Small blisters or bruises on the breasts Mild to moderate discomfort of nipples or breasts
	0	Engorged Cracked, bleeding, large blisters or bruises Severe discomfort
H = Hold	2	No assistance requirement for staff Mother can position or hold the baby
	1	Minimal assistance Teach one side and the mother does other Staff helps and the mother takes over the feeding
	0	Full assistance (staff holds the infant at the breast)

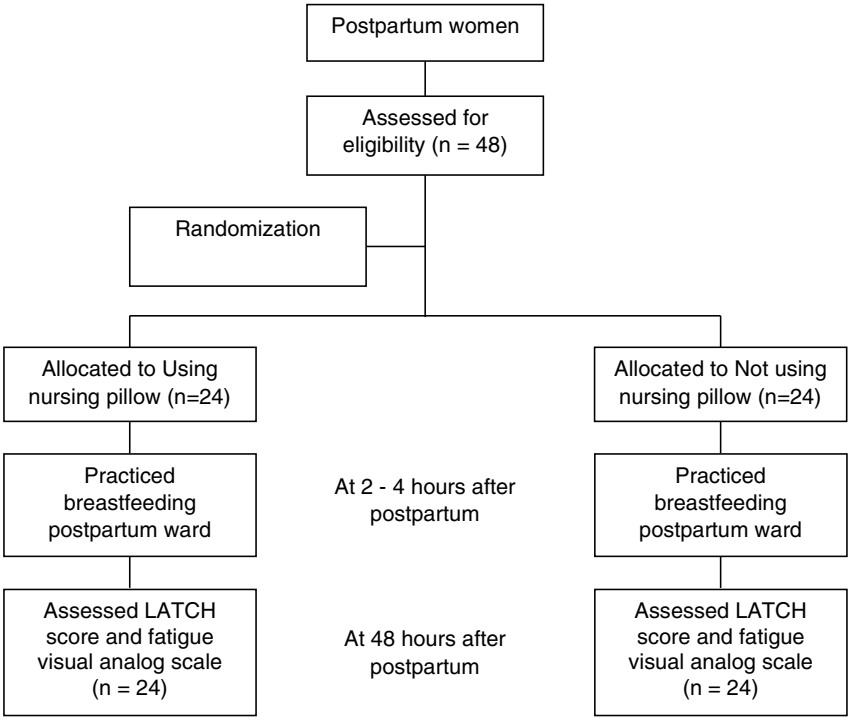

Fig. 1. Flow diagram of participants through the study.

Results

Considering all the data regarding the 48 postpartum women included in the study. The demographic data is shown in Table 2. The percentage of multiparous was 64.6%. The demographic data concerning the breastfeeding women who used and didn't use a nursing pillow was similar. There were no statistically significant differences in maternal age, occupation, marital status, religion, body mass index, gravida, nipple length, gestational age, and birth bodyweight.

The Mean LATCH score of breastfeeding women who used a nursing pillow was 8.48 ± 0.71. The mean LATCH score of breastfeeding women did not was 8.00 ± 0.74. The mean difference was 0.48 (95% confidence interval, 0.06 to 0.90; p = 0.027). The results are in Table 3. The primary outcome was statistically significant.

When further analyzing the data, the higher LATCH scores in the intervention group were attributable to the L-Latch, and A-audible swallowing. According to the L-Latch, 18 participants received full marks, compared to 15 in the control group. For the A-audible swallowing, 18 participants got full marks in the intervention group compared to 11 in the control group. However, it noted that the frequency of the highest scores of the C-Comfort in the intervention group was less than in the control group. The score of H-Hold was not different between the group.

The median and interquartile range fatigue visual analog scale of breastfeeding women who used a nursing pillow was 0.15 (0.0 - 1.1), while the median and interquartile range fatigue level of those who did not was 2.7 (1.25 - 3.7); p < 0.001. The results are shown in Table 4. The secondary outcome was statistically significant.

Table 2. Demographic data regarding breastfeeding women who used and didn't use a nursing pillow.

Demographic data	Used a nursing pillow (n = 24)	Didn't use a nursing pillow (n = 24)	p value
Age (years)	27.5±4.5	25.9± 5.2	0.26
Occupation, n (%)			0.16
Housework	4 (16.7%)	5 (20.8%)	
Student	0 (0%)	2 (8.3%)	
Employee	2 (8.3%)	7 (29.2%)	
Government officer	3 (12.5%)	1 (4.2%)	
Private business	9 (37.5%)	4 (16.7%)	
Private employee	6 (25%)	5 (20.8%)	
Marital status, n (%)			0.64
Married	21 (87.5%)	22 (91.7%)	
Single	3 (12.5%)	2 (8.3%)	
Religion, n (%)			0.303
Buddhist	17 (70.8%)	20 (83.3%)	
Muslim	7 (29.2%)	4 (16.7%)	
Body mass index (kg/m2)	22.6 (19.0-24.4)	19.9 (16.9-26.1)	0.99
Gravida, n (%)			0.76
Primigravida	9 (37.5%)	8 (33.3%)	
Multiparous	15 (62.5%)	16 (66.7%)	
Nipple length (mm)	10 (8.5-10)	10 (9-10.5)	0.95
Gestational age (weeks)	38.6 (37.9-39.2)	38.6 (37.9-39.2)	0.69
Birth weight (grams)	3031.7 ± 303.5	3025.4 ±324.3	0.95

Table 3. Comparisons of the LATCH scores between breastfeeding women who used and didn't use a using nursing pillow.

Outcome	Used a nursing pillow (n = 24) (mean ± SD)	Didn't use a nursing pillow (n = 24) (mean ± SD)	Mean difference	95% CI	p value
LATCH score	8.48 ± 0.71	8.00 ± 0.74	0.48	0.06 - 0.90	0.027

* Independent t-test
CI: confidence interval, SD: standard deviation

Table 4. Comparisons of the fatigue level between breastfeeding women who used and did not use a nursing pillow.

Outcome	Used a nursing pillow (n = 24) median (IQR)	Didn't use a nursing pillow (n = 24) median (IQR)	p value
Fatigue level	0.15 (0.0 - 1.1)	2.7 (1.25 - 3.7)	< 0.001

* Mann-Whitney U test
IQR: interquartile range

Discussion

Exclusive breastfeeding at least six months after birth is a strategic health policy. The correct breastfeeding technique is the crucial key to success. A LATCH score worldwide is used to assess breastfeeding quality. Many studies tried to find a way to improve a LATCH score that may advocate exclusive breastfeeding[15,16].

The nursing pillow is a popular household modality to correct maternal and infant positions during breastfeeding. We found that the postpartum women who used a U-shape nursing pillow had a statistically significant higher LATCH score. A reasonable explanation for these findings is that the nursing pillow helps support the infant's weight, allowing the head and body to stay on the same axis. An appropriate position improves breastfeeding comfort and results in the proper breastfeeding technique[17,18]. The mean difference was 0.48. It mainly increased from the L-Latch and the A-Audible swallowing. However, The LATCH scores differed statistically without clinical significance.

The Latch process consists of rooting, gaping, sealing, and sucking behavior. The previous study reported that proper suckling habits reduce nipple pain[8]. However, this study found that the proportion of the highest scores of C-Comforts in the control group was higher.

We also discovered that the postpartum women who used a nursing pillow had a fatigue level that was assessed by a visual analog scale significantly lower than those who didn't. The median fatigue level of breastfeeding women who used one was 0.15, whereas the other group averaged 2.7. The nursing pillow seems to help create a relaxed body position during breastfeeding. Such support decreases fatigue in the mother's arms, shoulders, neck, and back[19]. This finding correlated with a previous study that showed a significant decline in maternal discomfort among postpartum women using breastfeeding pillows[13].

The strength of our study was a randomized, controlled trial and the LATCH scores are a standardized criterion. We used the modified-cradle method in all participants to eliminate the potential confounding factor. The limitation of this study was that the intervention was not blinded; however, we had the LATCH scores determined by two well-trained breastfeeding nurses to minimize any bias. Several scoring tests were performed to ensure consistency before the beginning of the study. It is worth noting that there was also an opportunity of using the other types of pillows in the control group. This may result in the LATCH scores between the two groups not being much different.

For further study, we recommend randomized studies to compare different nursing pillows' LATCH scores and other additional relevant secondary outcomes, such as nipple pain and other lactation problems of all participants to cover all dimensions of the study results. Furthermore, other important variables related to successful breastfeeding might be needed, such as the start time of breastfeeding, frequency of breastfeeding.

Conclusion

The groups of breastfeeding women who used the U-shape nursing pillow had a higher LATCH score than the control group.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Causes of Secondary Amenorrhea: A report of 437 cases in Thailand

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ABSTRACT

Objectives: The aim of this study was to determine the prevalence of etiologic causes of secondary amenorrhea in Thailand.

Materials and Methods: A retrospective study was performed using 437 complete medical records of women with secondary amenorrhea who visited the Gynecologic Endocrinology clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand from April 1999 to October 2020.

Results: At the time of registration at our clinic, the patients had an average age of 28.7 ± 7.7 years. The median duration of amenorrhea was 8 months (range three months to 228 months). The majority of patients were nulliparous (70%). The average body mass index (BMI) was 25.2 ± 6.7 kg/m^2. More than half of all patients were overweight (11.2%) and obese (42.6%). Patients with polycystic ovary syndrome (PCOS) had the highest BMI. The four most common causes of secondary amenorrhea were PCOS (30.2%), anovulation (27.2%), hyperprolactinemia (9.8%), and premature ovarian insufficiency (9.2%). Other etiologies were diverse and less frequent. Two thirds of etiologies of secondary amenorrhea were in compartment four (67.5%). The prevalence of causes of secondary amenorrhea in compartment two (9.2%) and three (10.1%) was similar. The uterine cause and outflow tract obstruction was the least common cause of secondary amenorrhea (8.0%) of all four compartments. Postpill amenorrhea was found in 6.4% of patients. Meanwhile, thyroid disorder was the cause of secondary amenorrhea in 5% of patients.

Conclusion: The most common causes of primary and secondary amenorrhea were different. The most common cause of secondary amenorrhea in this study was PCOS. Further studies are required to determine the difference in causes of secondary amenorrhea in different nations.

Keywords: secondary amenorrhea, polycystic ovary syndrome, anovulation, hyperprolactinemia, premature ovarian insufficiency.

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สาเหตุของภาวะขาดระดูชนิดทุติยภูมิ: รายงานผู้ป่วย 437 รายในประเทศไทย

มุกประดับ ดารกมาศ, ประสงค์ ตันมหาสมุทร, กิติรัตน์ เตชะไตรศักดิ์, มณี รัตนไชยานนท์, สุชาดา อินทวิวัฒน์, ธันยารัตน์ วงศ์วนานุรักษ์, ปณิชา จันทราพานิชกุล และณิชมน ปิงกุล

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาความชุกของสาเหตุต่าง ๆ ของภาวะขาดระดูทุติยภูมิในประเทศไทย*

วัสดุและวิธีการ*: การศึกษาเชิงพรรณนาโดยการสืบค้นเวชระเบียนของสตรีที่มีภาวะขาดระดูทุติยภูมิ 437 คน ที่มารับการตรวจที่คลินิกต่อมไร้ท่อทางนรีเวช ภาควิชาสูตศาสตร์ นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล ประเทศไทย ตั้งแต่เดือนเมษายน พ.ศ. 2542 ถึงเดือนตุลาคม พ.ศ.2563*

ผลการศึกษา*: อายุเฉลี่ยของผู้ป่วย 28.7 ± 7.7 ปี ค่ามัธยฐานของระยะเวลาที่ขาดระดูเท่ากับ 8 เดือน (ช่วงระหว่าง 3 - 228 เดือน) ผู้ป่วยส่วนใหญ่ยังไม่มีบุตร (ร้อยละ 70) ดัชนีมวลกายเฉลี่ยเท่ากับ 25.2 ± 6.7 กิโลกรัมต่อตารางเมตร ผู้ป่วยจำนวนมากกว่าครึ่งหนึ่งมีน้ำหนักตัวเกิน (ร้อยละ 11.2) และอ้วน (ร้อยละ 42.6) ผู้ป่วยในกลุ่มอาการถุงน้ำรังไข่หลายใบมีดัชนีมวลกายสูงที่สุด สาเหตุของภาวะขาดระดูทุติยภูมิที่พบบ่อยที่สุด 4 อันดับแรก ได้แก่ กลุ่มอาการถุงน้ำรังไข่หลายใบ (ร้อยละ 30.2) ภาวะไม่ตกไข่ (ร้อยละ 27.2) ภาวะโปรแลกตินในเลือดสูง (ร้อยละ 9.8) และภาวะรังไข่ทำงานบกพร่องก่อนวัย (ร้อยละ 9.2) สาเหตุอื่น ๆ พบได้น้อย สองในสามของสาเหตุของภาวะขาดระดูทุติยภูมิอยู่ในคอมพาร์ตเมนท์สี่ (ร้อยละ 67.5) ความชุกของสาเหตุของภาวะขาดระดูทุติยภูมิในคอมพาร์ตเมนท์สอง (ร้อยละ 9.2) และคอมพาร์ตเมนท์สาม (ร้อยละ 10.1) ใกล้เคียงกัน คอมพาร์ตเมนท์ที่มีสาเหตุจากมดลูกและการอุดกั้นของทางออกพบได้น้อยที่สุด (ร้อยละ 8) ภาวะขาดระดูหลังหยุดยาคุมกำเนิดพบได้ ร้อยละ 6.4 ความผิดปกติของไทรอยด์พบเป็นสาเหตุของภาวะขาดระดูทุติยภูมิได้ร้อยละ 5*

สรุป*: สาเหตุที่พบบ่อยของภาวะขาดระดูปฐมภูมิและทุติยภูมิแตกต่างกัน สาเหตุของภาวะขาดระดูทุติยภูมิที่พบได้บ่อยที่สุดในการศึกษานี้คือกลุ่มอาการถุงน้ำรังไข่หลายใบ ควรทำการศึกษาเพิ่มเติมถึงสาเหตุของภาวะขาดระดูทุติยภูมิในประชากรที่มีเชื้อชาติแตกต่างกัน*

คำสำคัญ*: ภาวะขาดระดูทุติยภูมิ, กลุ่มอาการถุงน้ำรังไข่หลายใบ, ภาวะไม่ตกไข่, ภาวะโปรแลกตินในเลือดสูง, ภาวะรังไข่ทำงานบกพร่องก่อนวัย*

Introduction

Secondary amenorrhea is defined as no menses for a time interval of at least three previous cycles or no menses over a six-month period[1]. The diagnoses of primary and secondary amenorrhea differ. However, some conditions present as primary or secondary amenorrhea such as premature ovarian insufficiency (POI), polycystic ovary syndrome (PCOS), hyperprolactinemia, and pregnancy. A functioning hypothalamic-pituitary-ovarian (HPO) axis along with a normal genital outflow tract and uterus is required for menstrual function. Any disruption or abnormality to the organ can result in amenorrhea. The causes of amenorrhea can be categorized according to the site or level of disorder as compartment I-IV.

A careful review of patient history and physical examination is necessary to appropriately investigate, diagnose, and treat secondary amenorrhea. Laboratory investigations are based on data from the medical history and physical examination[1].

A few reports on the causes of secondary amenorrhea have been published. In 1986, Reindollar et al shared the results of a study in which 262 American patients had adult-onset amenorrhea[2]. This study showed that hypothalamic suppression followed by chronic anovulation, and then hyperprolactinemia and ovarian failure were the most frequently encountered etiologies. Another large case series by Kwon et al in 2014 showed that PCOS, POI, and nutrition-related hypogonadotropic hypogonadism were the three most common causes of secondary amenorrhea in Korean patients[2]. Since there is a difference in the cause of secondary amenorrhea between Western and Eastern populations, the aim of this study was to determine the prevalence of etiologic causes of secondary amenorrhea in Thailand.

Materials and Methods

This retrospective study was carried out at the Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The study protocol was approved by the Siriraj Institutional Review Board (SIRB) (certificate of approval no. Si 299/2021). Our study's anonymous retrospective design negated the need to obtain written informed consent from the participants.

The sample size was calculated using a formula to estimate a single proportion. When the precision was 0.05, α = 0.05, and the prevalence of PCOS among women presenting with secondary amenorrhea from the study by Kwon et al was 48.4%[2], the sample size plus 10% allowance for incomplete data was 422.

We reviewed the medical records of 865 women with secondary amenorrhea who registered at our clinic between April 1999 and October 2020. Of this group, complete medical histories and physical examinations for adequate investigation for diagnosis was available for 437 cases who then became eligible for this report.

The process of secondary amenorrhea diagnosis at our institute was conducted as follows: 1. Review of patient history, including the chief complaint, present condition, and past and family history, 2. Physical examination, including general examination and rectal and/or pelvic examination (PR/PV), 3. Laboratory investigations: Urine pregnancy test to rule out pregnancy if indicated. Serum thyroid stimulating hormone (TSH) and prolactin was the initial laboratory test along with the progestin challenge test. Further investigations depended on results

from the initial step, including estrogen- progestin challenge test, serum follicle stimulating hormone (FSH), estradiol, total testosterone, pelvic ultrasonography, saline infusion sonohysterography, imaging of pituitary and hypothalamus, karyotype, and autoimmune status.

According to the revised Rotterdam 2003 criteria[3], PCOS is diagnosed if two of the following criteria are met: clinical and biochemical signs of hyperandrogenism, oligo or anovulation, and polycystic ovaries on ultrasonography. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumor, and Cushing syndrome, must be excluded. Before the Rotterdam 2003 criteria, we diagnosed PCOS using the following criteria: chronic anovulation and clinical and/or biochemical signs of hyperandrogenism, and exclusion of other etiologies.

Statistical analysis

All data analysis was performed using SPSS Statistics for Windows version 17 (SPSS, Inc., Chicago, IL, USA). The outcomes were reported as frequency and percentage. The Kolmogorov-Smirnov test was used to test the distribution of continuous data. Normally, distributed continuous data was presented as mean ± standard deviation (SD), and non-normally distributed continuous data was given as median and range.

Results

A total of 437 patients were eligible for the present study. By the time of registration at our clinic, the average age of patients was 28.7 ± 7.7 years. The average body mass index (BMI) was 25.2 ± 6.7 kg/m^2. More than half of all patients were overweight (11.2%) and obese (42.6%). Patients with PCOS had the highest BMI. The median duration of amenorrhea was eight months (range three months-228 months). The majority of the patients were nulliparous (70%).

Table 1 demonstrates the causes of secondary amenorrhea and clinical features of patients. The four most common causes were PCOS (30.2%), followed by anovulation (27.2%), hyperprolactinemia (9.8%) and POI (9.2%). Other etiologies were diverse and less frequent. Two thirds of the etiologies of secondary amenorrhea were in compartment four (67.5%). The prevalence of the causes of secondary amenorrhea in compartment two (9.2%) and three (10.1%) were similar. Uterine cause and outflow tract obstruction was the least common cause of secondary amenorrhea (8.0%) of all the four compartments. Tuberculous endometritis was found in one patient.

Most causes related to POI were idiopathic (60%), and they were attributed to chemotherapeutic agents, ovarian operation, chromosome abnormality, and autoimmune disease. The patients with autoimmune disease included systemic lupus erythematosus (7 cases), autoimmune thyroiditis (2 cases) and Wegener granulomatosis (1 case).

Hyperprolactinemia was the most common cause in compartment three. Meanwhile, the most common cause of hyperprolactinemia was drug induced hyperprolactinemia (41.9%). Pituitary adenoma was found in 32.6% of hyperprolactinemic patients. One patient with craniopharyngioma developed panhypopituitarism after tumor removal.

Postpill amenorrhea was found in 6.4% of patients. Meanwhile, thyroid disorder was the cause of secondary amenorrhea in 5% of patients.

Table 1. The causes of secondary amenorrhea and clinical features of patients.

Cause	Number (%)	Age at registration (years)	BMI (kg/m²)	Duration of amenorrhea (month)	
		mean ± SD	mean± SD	median	[min, max]
Compartment 1	**35 (8.0)**				
Cervical stenosis	19 (4.3)	31.1 ± 5.4	24.1 ± 3.8	9	[3, 117]
Uterine synechiae	16 (3.7)	32.1 ± 6.4	22.1 ± 3.1	12	[3, 120]
Compartment 2	**40 (9.2)**				
Premature ovarian insufficiency	40 (9.2)	32.0 ± 6.5	21.6 ± 3.5	12	[3, 120]
Idiopathic	24 (5.5)	32.4 ± 5.8	20.8 ± 2.7	10	[3, 120]
Chemotherapy induced	2 (0.5)	30 ± 15.6	25.6 ± 7.7		[8, 36]
Ovarian surgery related	2 (0.5)	38 ± 0.0	23.8 ± 2.1		[4, 6]
Autoimmune	10 (2.3)	32.5 ± 7.1	22.6 ± 4.2	18	[3, 60]
Chromosomal abnormality (47,XXX and 46,XX9qh+)	2 (0.5)	26.0 ± 2.8	20.4 ± 3.8		[7, 36]
Compartment 3	**44 (10.1)**				
Hyperprolactinemia	43 (9.8)	29.5 ± 7.5	24.8 ± 5.4	7	[3, 120]
Pituitary adenoma	14 (3.2)	31.4 ± 5.8	24.7 ± 5.4	12	[4, 108]
Drug induced	18 (4.1)	27.5 ± 8.5	24.2 ± 4.8	5.5	[3, 36]
Idiopathic	11 (2.5)	30.6 ± 7.5	25.6 ± 6.9	12	[3, 120]
Panhypopituitarism	1 (0.2)	20	27.3	24	
Compartment 4	**295 (67.5)**				
Polycystic ovary syndrome	132 (30.2)	24.8 ± 6.5	28.3 ± 8.1	7	[3, 228]
Anovulation	119 (27.2)	29.1 ± 8.3	25.0 ± 7.2	8	[3, 228]
Stress related	4 (0.9)	27.3 ± 10.5	20.3 ± 4.1	6	[3, 12]
Weight changes related	37(8.5)	27.8 ± 7.0	27.8 ± 8.5	10	[3, 72]
Chronic disease	11 (2.5)	30.9 ± 10.8	24.2 ± 6.9	12	[3, 60]
Idiopathic	67 (15.3)	29.5 ± 8.3	23.6 ± 5.5	7	[3, 228]
Hypogonadotropic hypogonadism	17 (3.9)	29.9 ± 7.0	22.6 ± 5.6	12	[3, 96]
Postpill amenorrhea	28 (6.4)	31.9 ± 6.5	24.7 ± 5.8	5	[3, 12]
Other	**22 (5.0)**				
Hypothyroidism	16 (3.7)	35.7 ± 7.0	24.1 ± 3.2	7	[3, 48]
Hyperthyroidism	6 (1.4)	28.3 ± 9.4	22.9 ± 2.6	11	[6, 84]
Total	**437 (100%)**	28.7 ± 7.7	25.2 ± 6.7	8	[3, 228]

Data are presented as mean ± standard deviation, median (interquartile range), or number (percent) and [95% confidence interval].
Data were analyzed using: (a) one-way analysis of variance; (b) Kruskal-Wallis H, or (c) Chi-square test.
Each patient might experience more than one adverse event.
CI: confidence interval, BMI: body mass index

Discussion

This study evaluated the etiologies of secondary amenorrhea in 437 patients. The four most common causes of amenorrhea were PCOS (30.2%), anovulation (27.2%), hyperprolactinemia (9.8%), and POI (9.2%). This contrasts with our earlier study of 295 women with primary amenorrhea in which the most common etiologies were Müllerian agenesis, gonadal dysgenesis, and hypogonadotropic hypogonadism[4]. The difference in etiologies between primary and secondary amenorrhea was consistent with results of the American and Korean

studies[2, 5]. However, the frequency and order of etiology in our study was different.

As seen in the Korean study[2], PCOS was the most common cause of secondary amenorrhea in our study. However, the prevalence of PCOS in our study was lower than in the Korean series (30.2% vs 48.4%). In addition, other common causes differed as well. The second and third most common causes in the Korean study were POI (14.0%), and nutrition-related hypogonadotropic hypogonadism (8.3%). The average age at registration in the Korean study was 24.6 years, which was younger than in this study.

However, both studies were in contrast to a 1986[2] study by Reindollar et al, which revealed that the four most common causes of secondary amenorrhea in the American population were hypothalamic suppression (33.5%), chronic anovulation (28%), hyperprolactinemia (14%), and ovarian failure (12%). Hypogonadotropic hypogonadism was found in only 3.9% of patients in this study and 8.3% in the Korean study. More than half of American patients (54%) had hypogonadism while only 13% and 22% had the condition in this study and the Korean study. The second to fourth most common etiologies in the American study had a similar frequency and order to observations in this study. Postpill amenorrhea occurred in 29% of all patients in the American study, which seemed high and was more than the observation in this study (6.4%). The average age of presentation in the American study and our study was similar (26.4 vs 28.8 years). In the American study, the authors included PCOS into the chronic anovulation group. The most common cause of hypothalamic suppression in the American and Korean studies was associated to anorexia nervosa and weight loss[2, 5]. Only three patients with anorexia nervosa were found in this study. This difference may be due to variations in prevalence of anorexia nervosa, socio-cultural influences that focus on body image and weight in young women[6, 7], and also physical and emotional stressors[8].

PCOS is characterized by menstrual disturbances, ranging from abnormal uterine bleeding to oligomenorrhea and amenorrhea, hyperandrogenism, and infertility. PCOS patients are more likely to present with oligomenorrhea (76%) than amenorrhea (24%)[9, 10]. The symptoms often occur first at menarche, but signs of androgen excess may not become evident until several years later and these signs increase over time[11].

In North America, 75% of women with PCOS are obese[12], while 6.8% and 58.3% of patients with PCOS in this study were overweight and obese, respectively.

Consistent with the American and Korean series[2, 5], the prevalence of an abnormal karyotype in POI of secondary amenorrhea appeared low compared to cases of gonadal dysgenesis causing primary amenorrhea[4]. Most causes related to POI were idiopathic, and attributed to chemotherapeutic agents, ovarian operations and autoimmune disease[13, 14]. Autoimmune disease related to POI in Korean study and our study was similar[2].

Hyperprolactinemia was the most common cause of secondary amenorrhea in compartment three. Hyperprolactinemia was 14% in the American series[5] and 7.8 % in Korean series[2], which was quite similar to the 9.8% noted in this study. In our study, the most common cause of hyperprolactinemia was drug induced hyperprolactinemia (41.9%). Pituitary adenoma was found in 32.6% of hyperprolactinemic patients. Thyroid disorder was reported as 1.5% in both the American and Korean series[2, 5], but was 5% in our study. The data provides support for the practice of obtaining a serum prolactin and TSH determination in women with amenorrhea. Serum prolactin and TSH combined with the progestin challenge test is the appropriate initial investigation for secondary amenorrhea.

Secondary amenorrhea has a significantly less impact on future well-being than was reported for patients whose amenorrhea developed as a result of pubertal aberrancy. The etiologies of secondary amenorrhea were largely different from those of primary amenorrhea. Analysis of morbidity data

indicated that secondary amenorrhea presents less significant detrimental effects on the quality of life, including fertility, than primary amenorrhea[5, 15]. However, early diagnosis, treatment, and counseling remain essential for all patients.

This study has some mentionable limitations. First, the present study was a retrospective chart review, which is a study design known to be associated with missing and/or incomplete data. Second, the study was conducted in a tertiary care university hospital, and thus, the study population was affected by patient's preference, referral patterns, and what referring physicians were comfortable taking care of.

Conclusion

In conclusion, the most common causes of primary and secondary amenorrhea are different. The most common cause of secondary amenorrhea in this study was PCOS, which was similar to the Korean study[2], but contrasts the American study[5]. Thus, ethnic, environmental, socio-cultural, and genetic factors may play a role in the development of amenorrhea. Further studies are required to determine the difference in causes of secondary amenorrhea in different nations.

Acknowledgments

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Changes of Ovarian Reserve after Hysterectomy for Non-oncologic Conditions in Reproductive-aged Women: A prospective study

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ABSTRACT

Objectives: To assess the impact of hysterectomy on the ovarian reserve markers in reproductive-aged women.

Materials and Methods: This prospective cohort study was conducted from May 2021 to April 2022. Reproductive-aged women who underwent hysterectomy without ovarian surgery due to benign conditions at Rajavithi Hospital were recruited. Ovarian reserve markers were compared between the date before surgery and 12 weeks following hysterectomy by measurement of serum anti-Müllerian hormone (AMH), antral follicle count (AFC) and ovarian volume (OV).

Results: Fifty-five reproductive-aged women were enrolled. Different proportion (DP) between serum AMH at preoperative and 12 weeks postoperative was decreased after hysterectomy (DP 22.5%, $p = 0.001$). The antral follicle count (AFC) and ovarian volume (OV) were also decreased (DP 33.3%, $p < 0.001$, and 20.0%, $p < 0.001$, respectively). Nonetheless, surgical outcomes and menopausal symptoms were not different.

Conclusion: Hysterectomy without ovarian surgery affects the ovarian reserve at 12 weeks post operation without significantly changing of menopausal symptoms. However, other long-term consequences from accelerated ovarian aging should be investigated.

Keywords: ovarian reserve, anti-mullerian hormone, ovarian volume, antral follicle count, hysterectomy.

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การทำงานของรังไข่ที่เปลี่ยนไปหลังการผ่าตัดมดลูกด้วยภาวะที่ไม่ใช่มะเร็งในสตรีวัยเจริญพันธุ์: การศึกษาแบบไปข้างหน้า

ณัชชา ศิลป์ไพบูลย์พานิช, พฤฒพร มณีรัตน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลกระทบของการตัดมดลูกต่อค่าการทำงานของรังรังไข่ในสตรีวัยเจริญพันธุ์*

วัสดุและวิธีการ: *การศึกษาวิจัยแบบไปข้างหน้าดำเนินการในสตรีวัยเจริญพันธุ์ที่เข้ารับการผ่าตัดมดลูกโดยไม่มีการผ่าตัดรังไข่เนื่องจากสาเหตุที่ไม่ใช่มะเร็งในโรงพยาบาลราชวิถี ตั้งแต่เดือนพฤษภาคม พ.ศ. 2564 ถึงเดือนเมษายน พ.ศ. 2565 โดยเปรียบเทียบค่าการทำงานของรังไข่วันก่อนการผ่าตัดและ 12 สัปดาห์หลังการตัดมดลูก โดยวัดระดับฮอร์โมนแอนตี้มูลเลอเรียน (anti-Müllerian hormone: AMH) ในเลือด และตรวจอัลตร้าซาวด์ทางช่องคลอดเพื่อวัดจำนวนฟองไข่ (antral follicle count: AFC) และวัดปริมาตรของไข่ (ovarian volume: OV)*

ผลการศึกษา: *จากการศึกษาในสตรีวัยเจริญพันธุ์จำนวน 55 คน พบว่าฮอร์โมนแอนตี้มูลเลอเรียนลดลงเมื่อเปรียบเทียบก่อนผ่าตัดและหลังผ่าตัด 12 สัปดาห์ โดยสัดส่วนที่แตกต่างกัน (Different proportion: DP) เฉลี่ยอยู่ที่ร้อยละ 22.5 ($p = 0.001$) เช่นเดียวกับจำนวนฟองไข่ และปริมาตรของไข่ ที่ลดลงด้วยโดยมีสัดส่วนที่แตกต่างกัน ร้อยละ 33.3% และร้อยละ 20.0 ($p < 0.001$ และ $p < 0.001$) ตามลำดับ อย่างไรก็ตาม ผลข้างเคียงจากการผ่าตัด และอาการของการหมดประจำเดือนไม่ได้เปลี่ยนแปลงอย่างมีนัยสำคัญ*

สรุป: *การตัดมดลูกโดยไม่ได้ผ่าตัดรังไข่มีผลต่อค่าการทำงานของรังไข่หลังการผ่าตัด 12 สัปดาห์ โดยไม่มีการเปลี่ยนแปลงของอาการของการประจำเดือนอย่างมีนัยสำคัญ อย่างไรก็ตามควรมีการศึกษาผลจากการผ่าตัดในระยะยาวต่อไป*

คำสำคัญ: *ค่าการทำงานของรังไข่, ฮอร์โมนแอนตี้มูลเลอเรียน, จำนวนฟองไข่, ปริมาตรของไข่, การตัดมดลูก*

Introduction

Hysterectomy is the most common gynecologic surgery nowadays. The mean age of patients who underwent hysterectomy was 40.5 years old[1] and tends to increase in older ages. The most common indications for hysterectomy are symptomatic leiomyoma (51.4%), abnormal uterine bleeding (41.7%) and endometriosis (30%)[2]. The surgical approaches to hysterectomy comprise total abdominal hysterectomy, vaginal hysterectomy and minimally invasive procedures such as laparoscopic hysterectomy, robotic-assisted laparoscopic hysterectomy and vaginal natural orifice transluminal endoscopic surgery (vNOTES)[2]. The optimal route of surgery is justified according to the suitability and benefit of each patient, the shape and size of the vagina and accessibility to the uterus, the extent of extrauterine disease, the size and shape of the uterus, comorbidity, preference of the informed patient, hospital devices and surgeon experience. Laparoscopic hysterectomy has a faster return to normal activity, shorter hospital stays, and fewer wound infections than laparotomy. Surgical complications, for example, surgical site infection, blood loss and adjacent organ injury were not significantly different between the open and laparoscopic approaches[2].

Another consequence of hysterectomy is the deterioration of ovarian function, even though the ovaries were preserved[3]. The etiology is believed to result from the ovarian branches of the uterine artery being damaged after hysterectomy, which leads to the disturbance of blood supply to the ovaries[4]. Advancing of ovarian aging would result in not only postmenopausal symptoms, but also long-term health effects from hypoestrogenism, such as, coronary artery disease, dementia and osteoporosis which negatively impact on the quality of life[5].

Ovarian function composes of reproductive and endocrine functions. Ovarian reserve markers are widely used to predict fertility outcomes of infertile patients, such as follicle stimulating hormone (FSH), estradiol (E2), inhibin B, anti-Müllerian hormone (AMH) and ultrasound for antral follicle count (AFC) or ovarian volume (OV)[6]. However, AMH was little intracycle variation and predicted ovarian reserve independent of menstrual cycle[7]. The previous study showed that AMH levels decreased up to 30% after three months of hysterectomy (1.08 ± 0.77 ng/ml and 0.78 ± 0.58 ng/ml respectively)[8].

The purpose of this study was to compare the different proportions (DP) or percentage changes of individual ovarian reserve markers, including serum levels of AMH combined with ultrasound measurements of AFC and OV in premenopausal women who underwent hysterectomy without oophorectomy.

Materials and Methods

Subject recruitment

This was a prospective cohort study that recruited reproductive-aged women from 25 to 50 years old who visited Rajavithi Hospital, Bangkok, Thailand, and underwent hysterectomy for non-oncologic conditions from May 2021 to June 2022. This study was approved by the Institutional Review Board of Rajavithi Hospital. (EC number 64067) No protocol amendments were made after the trial started.

Inclusion and exclusion criteria

The inclusion criteria consisted of female patients aged 25-50 who visited the Rajavithi hospital for a hysterectomy without ovarian surgery for non-oncologic conditions, were able to communicate in Thai, and were willing to participate in the research. If transvaginal sonography revealed dominant follicle, the participant was not included, because measurement of AFC is cycle dependent. Exclusion criteria were as follows: women who had amenorrhea for more than one year, had a history of salpingo-oophorectomy or ovarian surgery, had gynecologic malignancy, genetic or autoimmune diseases, received chemotherapy, brachytherapy

or radiation and received hormonal contraception within one year. Moreover, participants with an initial AMH lower than 0.05 ng/ml were also excluded because changes in AMH could not be compared.

Based on a previous study, a comparison of the AMH values before and after hysterectomy was used to calculate the sample size[8]. The mean difference of AMH was about 30%, therefore we determined that if the difference between AMH before and 3 months post-operation was exceeded 30%, it was significantly different. Using an alpha of 0.05 and a beta of 80%, the minimal sample size was 51 patients. On account of the 30% dropout rate and low level of AMH, 66 patients were enrolled in the study.

Data collection and ovarian reserve measurement

Enrolled participants were first interviewed by a researcher for demographic and relevant data, including previous pregnancy history, maternal menopausal age, menstrual characteristics, underlying diseases, current medication, smoking and previous surgical history. At one day before surgery patients' blood sample was collected in a lithium heparin tube for AMH and delivered to the laboratory department of Rajavithi Hospital to measure AMH level using chemiluminescent immunoassay system (MAGLUMI 2000; Snibe Co., Ltd). Transvaginal sonography for the antral follicle count and ovarian volume was performed by the investigator (Voluson S6, GE Healthcare Support Services) and ovarian volumes were the sum of both ovaries, calculated using the formula length × width × depth × 0.52. If preoperative AMH is less than 0.05 ng/ml and/or transvaginal sonography reveals a dominant follicle, the patients were excluded.

The surgical technique of the hysterectomy

Procedures for total abdominal hysterectomy (TAH) consisted of clamping of the round ligament, cut and ligated. Each utero-ovarian ligament was clamped, cut and ligated. The broad ligament was separated downward, and bladder was mobilized. The uterine artery was skeletonized and clamped at the isthmic portion of the uterus. The pedicle was cut, and suture ligated to ensure hemostasis. The cardinal ligament and uterosacral ligament were all clamped, and suture ligated consequently. The cervicovaginal angle was accessed and hysterectomy was done. Following the removal of the uterus, the vaginal stump was closed using the continuous lock technique. Finally, the abdominal wall was closed layer by layer[4].

The total laparoscopic hysterectomy (TLH) was performed using the same steps as TAH. The pneumoperitoneum was created by Veres needle, and the trocars were placed. Round ligaments, uteroovarian ligaments, uterine arteries, cardinal ligaments and uterosacral ligaments were coagulated and cut by bipolar electrocauterization. The uterus was removed through the vagina and the vaginal stump was closed via laparoscopy[4].

Postoperative data collection

Enrolled participants were undergoing surgery, and information about the surgery was recorded by the doctor who attended the surgery using a data record form. Prior to the surgery, they were informed and trained to record the form precisely. Afterwards, the patients were appointed in the 2nd week postoperatively to inquire about complications from surgery and menopausal symptoms. If the pathology results were malignant, they were excluded from further analysis. The final appointment was on the 12th week to reevaluate postmenopausal symptoms, receive blood tests for AMH and transvaginal sonography to measure AFC and OV. Owing to the absence of uterus, the exact date of the menstrual cycle was unpredictable. If the follow-up sonography revealed a dominant follicle, the patients were scheduled to repeat sonography in three weeks.

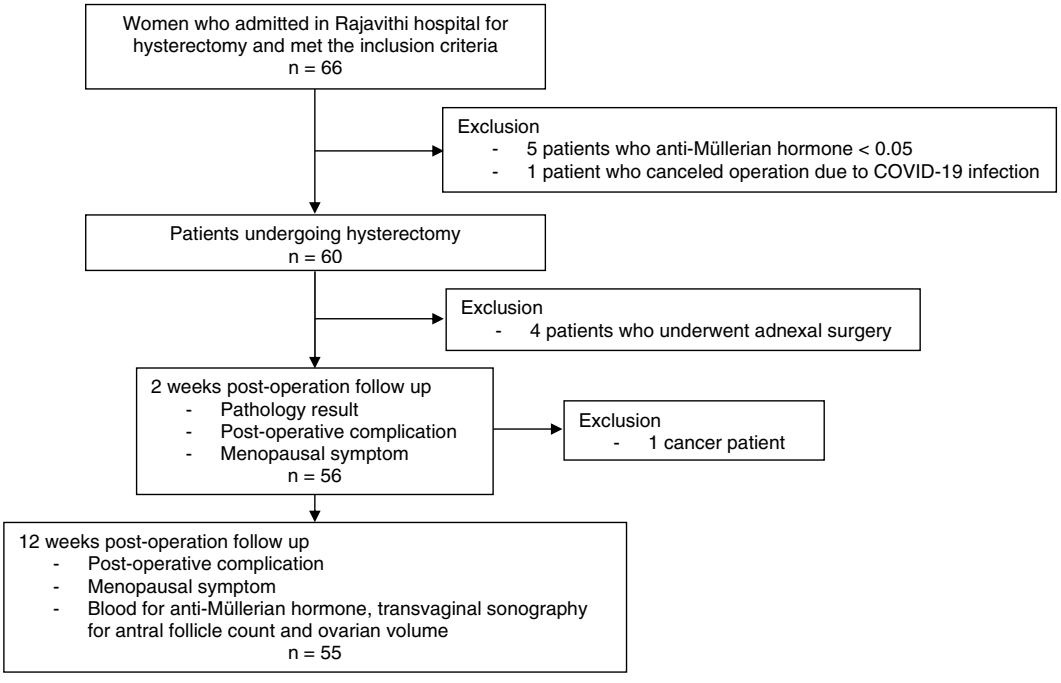

Fig. 1. Study flow diagram.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 26.0, SPSS Inc., IBM New York, USA). Numerical data were presented as the mean with standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of each variable. The categorical data were presented by proportion and percentage. The independent t-test, Wilcoxon signed rank test and McNemar test were used to compare continuous variables. A p value of < 0.05 was determined to be statistically significant.

Results

A total of 66 participants were enrolled between May 2021 and June 2022. Five participants were excluded due to AMH < 0.05 ng/ml and another patient that the operation was cancelled due to COVID-19 infection were excluded. From 60 patients who underwent surgery, four patients were excluded because an oophorectomy was performed, and another was excluded after the pathology result was cancer. Finally, 55 participants were eligible for the analysis. (Fig. 1.)

The demographic characteristics of patients in this study and information about the surgery are shown in Table 1. The average age of participants was 40.67 ± 4.51 years, with a mean body mass index (BMI) of 26.11 ± 7.5 kg/m^2. Twenty percent had a history of cesarean section and 16.4% had postpartum tubal sterilization. Regarding the operation, forty-seven patients (85.5 %) underwent hysterectomy with bilateral salpingectomy. Classified by surgical approach, 34 participants (61.8%) were undergoing TAH, and 21 participants (38.2%) were undergoing TLH. Uterine leiomyoma was the most common pathological diagnosis in 35 patients (63.6%). For the type of operation, 8 patients (14.5%) were hysterectomy, and 47 patients (85.5%) were hysterectomy with BS. During the operation, three patients experienced surgical complications; two patients had bladder injuries and excessive blood loss of more than 1,000 ml.

Table 1. Baseline characteristics of the patients.

Characteristics	
Age (years), mean ± SD	40.67 ± 4.51
BMI, (kg/m^2), mean ± SD	26.11 ± 7.5
- BMI > 30, n (%)	15 (27.3%)
Parity	
- Nulliparity, n (%)	24 (43.6%)
Maternal menopause age, (years), mean ± SD	50.82 ± 2.3
Previous surgery, n (%)	
- Cesarean section	11 (20.0%)
- Tubal resection	9 (16.4%)
Type of operation, n (%)	
- TAH	34 (61.8%)
- TLH	21 (38.2%)
Operation, n (%)	
- Hysterectomy	8 (14.5%)
- Hysterectomy with BS	47 (85.5%)
Operation time (minutes), mean ± SD	147.67 ± 41.89
Blood loss (ml), median (IQR)	200 (250)
Complication, n (%)	
- Blood loss > 1000 ml	2 (3.6%)
- Bladder injury	2 (3.6%)
Pathological diagnosis, n (%)	
- Myoma uteri	35 (63.6%)
- Adenomyosis	19 (34.5%)
- CIN 3	1 (1.8%)

Data were presented as mean ± standard deviation (SD), median (interquartile range (IQR)) and number (%)
BMI: body mass index, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, BS: bilateral salpingectomy, CIN: cervical intraepithelial neoplasia

The ovarian reserve markers revealed an AMH of 0.58 (18.1) ng/ml, an AFC of 7 (5) follicles, and an OV of 13.2 (8.2) ml as the median (IQR). Postoperative ovarian markers of AMH, AFC and OV were 0.4 (1.46) ng/ml, 4 (3) follicles and 9.2 (7.6) ml, respectively.

Overall changes in postoperative ovarian markers are shown in Fig. 2. AMH levels were significantly decreased with a median (IQR) DP of 22.47% (68.68), p = 0.001. Twenty-five patients (45.5%) had AMH level decreased ≥ 30%. In addition, AFC and OV were also significantly decreased by the median (IQR) DP of 33.33% (43.33) and 20.0% (25.95) respectively, p < 0.05.

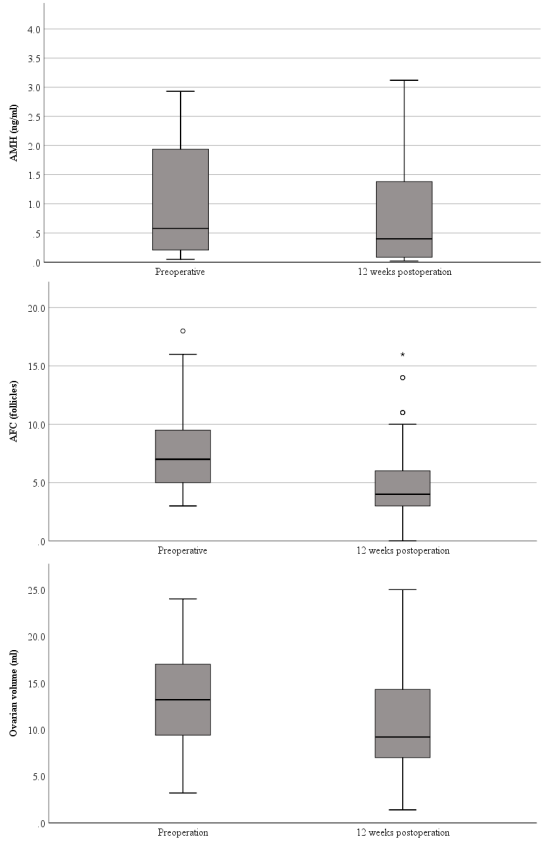

Fig. 2. Changes of ovarian reserve markers between preoperative and 12 weeks after hysterectomy.

Subgroup analysis was performed using logistic regression to estimate the factors associated with diminished AMH of more than 30% and found that BMI ≥ 28 kg/m^2 was the only factor that correlates with significantly declined AMH (odds ratio 1.11, p = 0.025). Subgroup analysis by the age of hysterectomy was not significant. Also, surgical variations such as surgical approach or opportunistic salpingectomy were not correlated with significantly diminished AMH. Nine participants (16.4%) and 10 participants (18.2%) had menopausal symptoms in the 2nd and 12th weeks, respectively. Postoperative wound infection occurred in two participants at two weeks with ongoing infection at 12 weeks and two participants had a wound dehiscence at two weeks.

Discussion

Hysterectomy has a significant effect on ovarian reserve markers with a median DP of 22.47%. 45.5% of them had AMH level decreased ≥ 30%. According to a previous study, AMH was considered to have significantly decreased by 0.27 ng/ml, or approximately 30% after three months of hysterectomy (1.08 ± 0.77 ng/ml and 0.81 ± 0.58 ng/ml, respectively). Furthermore, in another study, the mean AMH level after hysterectomy was 1.08 ± 0.94 ng/mL, which was significantly lower than the level in the control group (1.54 ± 1.10 ng/mL) (p = 0.016)[9]. The laboratory variation of AMH during the menstrual cycle is up to 30%[10]. Therefore, we determined that the reduction of AMH at least 30% was a significant level of DP[8]. The duration of our

study was 12 weeks, which was comparable with some previous studies[8], and another study showed no significant difference in AMH at 6 months compared with 2 months[11].

Not only AMH but also AFC and OV were affected. The AFC and OV were significantly lower, with median DP of 33.33% and 20%, respectively. Nevertheless, the previous study indicated that ovarian volume was unchanged after hysterectomy[9].

Higher BMI correlated with significantly lower AMH. It could be assumed that women with higher BMI might have endocrine disruptions including, steroidogenesis, metabolism, and inflammation, impaired folliculogenesis, and ovulatory potential, which affect the production of the AMH[12]. In addition, abnormal vascular function might potentiate the effects of vascular compromise after hysterectomy. However, participants of study had lower BMI, higher age and high baseline AMH could affect the changes of AMH after hysterectomy themselves. Due to the smaller sample size after subgroup analysis, the power of the study to determine each factor might be lacking.

Opportunistic salpingectomy was not correlated with significantly decreased AMH. According to the recommendation[2], bilateral salpingectomy was planned to prevent epithelial ovarian cancer, but in some patients, it was complicated by severe adhesion. The opportunistic salpingectomy was discontinued. The previous study showed no correlation between significantly decreased AMH and hysterectomy with or without BS after subgroup analysis[13]. Also, the surgical approach was not found to be associated with lower AMH in this study. Nevertheless, according to Cho et al, laparoscopic hysterectomy resulted in a reduction of AMH at two months after surgery (hazard ratio 4.147, 95% confidence interval 1.139-15.097)[11].

Short-term adverse events related to decreased ovarian function were reflected by menopausal symptoms. However, our study showed no significant correlations between significantly decreased AMH and menopausal symptoms. There has been reported that the lower AMH was associated with increased risk of vasomotor symptoms in postmenopausal women, but data regarding changes in AMH were not collected[14]. Vasomotor symptoms are caused by the fluctuation of estrogen, that correlation with dynamic change of AMH and vasomotor symptoms might be plausible. However, the incidence of postoperative vasomotor symptoms was low and the power to determine the correlation was lacking.

For the strength of the study, this is the first prospective cohort trial that investigated the effects of hysterectomy on AMH might be useful to validate the marker of ovarian endocrine factors to monitor patients underwent hysterectomy in the future. AMH was used as the primary outcome measure to avoid intracycle variation from other markers and it was objectively reliable. All patients had a complete blood test protocol to compare the differences in ovarian reserve markers individually. Nonetheless, owing to the conditions of the COVID-19 pandemic, the duration of the study was limited to only 12 weeks, which reflects only the effect of hysterectomy, but the consequences of decreased ovarian function might be in the long run. Thus, the long-term sequelae of hysterectomy on ovarian function could not be justified. AFC and OV exhibit intracycle variation. The exact date of the ultrasonographic evaluation was uncertain, particularly after the procedure.

Conclusion

Hysterectomy significantly decreased ovarian reserve markers; AMH, AFC and OV. However, even with significantly depleted AMH after hysterectomy, short term sequelae from hypoestrogenism were not increased. Further studies to monitor the long-term consequences of hysterectomy on decreased ovarian function should be explored.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence of and Factors Associated with Large Cesarean Scar Defects in Women at Six Weeks Postpartum

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ABSTRACT

Objectives: To demonstrate the prevalence and factors associated with a large Cesarean scar defect (CSD) in Thai postpartum women.

Materials and Methods: This was a cross-sectional study. The participants were enrolled for a postpartum sonographic examination at the sixth-week follow-up from August to December 2021. CSD was measured using a two-dimensional transvaginal ultrasound device. A large CSD was defined as having a height of ≥ 50% of the total myometrial thickness. The sonographer was blinded to the obstetric history until all parameters had been recorded.

Results: At six weeks postpartum, CSD was identified in 94 participants. There were 64 and 30 participants in the primary and repeat Cesarean section (CS) groups, respectively. The overall prevalence of large CSD was 22.3%. A large CSD was seen in 15.6% (10/64) and 36.7% (11/30) of the patients in the primary and repeated CS groups. The factors associated with large CSD were repeated CS (p = 0.002), cervical dilatation ≥ 6 cm at the time of CS (p = 0.023), and uterine retroflexion (p = 0.015) groups, with odds ratio of 8.85 (95% confidence interval (CI) 2.29-34.15), 5.84 (95%CI 1.28-26.71) and 4.40 (95%CI 1.33-14.55), respectively.

Conclusion: The overall prevalence of large CSDs was 22.3%. Repeated CS, uterine retroflexion, and cervical dilatation ≥ 6 cm at the time of CS had higher odds of developing a large CSD.

Keywords: cesarean section, uterine scar defect, ultrasound, postpartum.

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ความชุกและปัจจัยที่สัมพันธ์กับร่องแผลเป็นมดลูกขนาดใหญ่จากการผ่าคลอดที่หกสัปดาห์หลังคลอดบุตร

ณภัทร นิตยพันธ์, วิภาดา เหล่าสุขสถิตย์, กิตติพงษ์ คงสมบูรณ์, เมธาพันธ์ กิจพรธีรานันท์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกของร่องแผลเป็นมดลูกขนาดใหญ่และปัจจัยที่สัมพันธ์ในสตรีไทยหลังคลอด*
วัสดุและวิธีการ: *การวิจัยนี้ศึกษาแบบภาคตัดขวาง โดยผู้เข้าร่วมวิจัยจะได้รับการตรวจคลื่นเสียงความถี่สูงทางช่องคลอดแบบสองมิติ โดยนิยามร่องแผลเป็นมดลูกขนาดใหญ่เมื่อพบร่องที่มีความลึกมากกว่าหรือเท่ากับร้อยละ 50 ของความหนาชั้นกล้ามเนื้อมดลูกทั้งหมด ซึ่งผู้ตรวจคลื่นเสียงความถี่สูงจะไม่ทราบประวัติทางสูติกรรมของผู้เข้าร่วมวิจัย*
ผลการศึกษา: *ที่ 6 สัปดาห์หลังคลอด สามารถตรวจพบร่องแผลเป็นที่มดลูกบริเวณที่ผ่าตัดคลอดทั้งหมด 94 ราย โดยมีกลุ่มผ่าตัดคลอดครั้งแรก 64 ราย และกลุ่มผ่าตัดคลอดซ้ำ 30 ราย และมีความชุกร่องแผลเป็นขนาดใหญ่ทั้งหมดร้อยละ 22.3 โดยพบในกลุ่มผ่าตัดคลอดครั้งแรกร้อยละ 15.6 (10/64 ราย) และในกลุ่มผ่าตัดคลอดซ้ำร้อยละ 36.7 (11/30 ราย) ปัจจัยที่สัมพันธ์กับการพบร่องแผลเป็นขนาดใหญ่ ได้แก่ การผ่าตัดคลอดซ้ำ ($p = 0.002$) ปากมดลูกเปิดขยายมากกว่าหรือเท่ากับ 6 เซนติเมตร ($p = 0.023$) และ มดลูกคว่ำหลัง ($p= 0.015$) โดยเพิ่มความเสี่ยงเป็น 8.85 เท่า (95% confidence interval (CI) 2.29-34.15), 5.84 เท่า(95%CI 1.28-26.71) และ 4.40 เท่า (95%CI 1.33-14.55) ตามลำดับ*
สรุป: *ความชุกของร่องแผลเป็นมดลูกขนาดใหญ่หลังผ่าตัดคลอดบุตรร้อยละ 22.3 โดยมีปัจจัยที่สัมพันธ์ได้แก่ การผ่าตัดคลอดซ้ำ มดลูกคว่ำหลัง และ ปากมดลูกเปิดขยายมากกว่าหรือเท่ากับ 6 เซนติเมตรขณะผ่าคลอด*

คำสำคัญ: *ผ่าตัดคลอด ร่องแผลเป็นมดลูก คลื่นเสียงความถี่สูง หลังคลอดบุตร*

Introduction

Cesarean section (CS) is a lifesaving procedure which is mandatory in certain situations. The CS rate has increased worldwide in recent decades[1]. Cesarean scar defect (CSD), also known as uterine isthmocele or uterine niche, is an iatrogenic complication exclusive to CS. It is a discontinuity of the myometrium and behaves like a reservoir pouch at the site of a previous cesarean scar. The prevalence of CSD has been increasing with the CS rate, with a rate of 64.5% CSD at 6-12 months postpartum. Early scanning is recommended to locate the scar defect when it is more prominent[2].

A large CSD correlates with a higher prevalence of symptoms, such as postmenstrual spotting and chronic pelvic pain[3]. The range of associated complications is vast, ranging from abnormal uterine bleeding to life-threatening conditions such as uterine rupture and cesarean scar pregnancy[4]. Women with a large CSD are also reportedly at risk of uterine dehiscence[5] or placenta accreta spectrum[6-8]. These complications are associated with high morbidity and mortality.

Large CSDs have usually been investigated at six months postpartum. A recent study has followed CSD from six weeks to one year and concluded that its presence is consistent[9]. CSD is multifactorial and involves the interplay between genetic factors, maternal health, local microenvironment, suturing techniques, uterine habitus, and number of surgeries[10]. We aimed to investigate the effect of repeated CS on CSD, as it may alter myometrial healing. Previous reports have demonstrated the pathophysiology of repetitive tissue trauma in wound healing and inflammation[11]. We postulate that a large CSD can be detected as early as six weeks postpartum.

The primary outcome was the prevalence of a large CSD at six weeks postpartum. The secondary outcome was the association between repeated CS and a large CSD.

Materials and Methods

Participants

This was an analytical cross-sectional study. The project was approved by the institutional ethics committee (No: SWUEC-006/64) and was registered with the Thai Clinical Trials Registry (No: TCTR20210420004). Postpartum women who had undergone CS between August and December 2021 were recruited in the postpartum ward after the surgery. Information regarding the study was thoroughly explained to all participants. All participants provided informed consent to participate in the study after CS before they were discharged. All surgeons employed the same surgical technique. A low transverse incision and two-layer suturing technique (locking the first layer and non-locking the second layer) was performed in all patients.

A pilot study was conducted with 25 participants. The sample size was calculated using a two-independent proportion formula, where p1 represented patients with large CSDs after primary CS (0.05 [1/18]), p2 represented patients with large CSDs after repeated CS (0.28 [2/7]), and the ratio was 0.38. A total of 94 participants were recruited.

$$n_1 = \left[\frac{z_{1-\frac{\alpha}{2}}\sqrt{\bar{p}\bar{q}(1-\frac{1}{r})}+z_{1-\beta}\sqrt{p_1q_1+\frac{p_2q_2}{r}}}{\Delta} \right]^2$$

The participants were Thai and had undergone CS at our institution. The inclusion criteria were as follows: singleton pregnancy with a low transverse uterine incision, no history of uterine surgery other than CS, absence of uterine abnormality, absence of placenta previa or abnormally adherent placenta, and consent to participate. The exclusion criteria were as follows: failure to obtain all sonographic parameters, postpartum metritis, late postpartum hemorrhage, and loss to follow-up at 6 weeks (Fig. 1). All the surgeons employed similar surgical techniques and used monofilament sutures (1-0 chromic catgut) to repair the uterine incision.

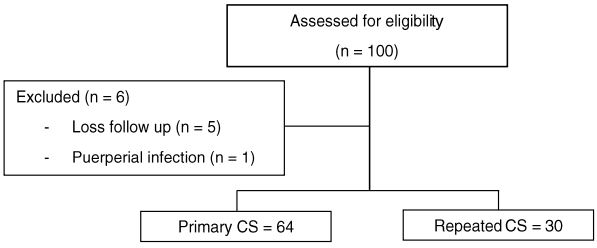


Fig. 1. Consort flow chart

Assessment of CSD

The sonographer was blinded to the patient's information during ultrasonography. Ultrasonography was performed by one sonographer (NN), who has completed a pelvic ultrasound workshop and is certified by a maternal-fetal medicine specialist. All measurements were reported on two-dimensional (2D) static images and were approved without disagreement. After ultrasonography, patient demographics, antenatal care information, inpatient records, and operative notes were collected. Transvaginal ultrasound (TVS) examinations were performed at six weeks postpartum using a Voluson™ P8 machine (GE Healthcare, Bangkok, Thailand). This timing allowed better visualization of the CSD without the additional need for instillation ultrasound. Uterine habitus was defined as retroflexion and anteflexion.

Sonographic protocol

The ultrasound protocol was adapted from that of Osser et al (2009)[12]. The TVS probe was pressed firmly into the cervix, without excessive pressure, to visualize the uterus in the midsagittal plane. The lower uterine segment occupied approximately ¾ of the ultrasound screen. The uterine incision site was examined for CSD. We collected the uterine position and CSD parameters (Fig. 2, 3). An indentation of at least 2 mm at the incision site was considered CSD. CSD parameters included the base, height (H), residual myometrial thickness (RMT), and total myometrial thickness (TMT). First, a line was drawn at the base of the triangular defect, which represented the base. Subsequently, the CSD apex was identified; a perpendicular line from the apex to the base of the CSD represented the CSD height. The RMT was defined as the distance from the apex of the CSD to the uterine serosa. The TMT was the normal uninvolved myometrium, located just cephalad to the scar defect and defined as the distance from the base of the CDS to the uterine serosa. Non-instillation ultrasonography was performed. Therefore, the shape of the CSD could not be categorized.

The percentage of the CSD height was calculated as (H/TMT) × 100. A value ≥ 50% was considered a 'large CSD'[4, 13]. Large CSDs were the focus of this study because they are associated with more severe complications[2].

In patients with large CSDs, we advised outpatient follow-up for six months and early first-trimester scanning in a subsequent pregnancy.

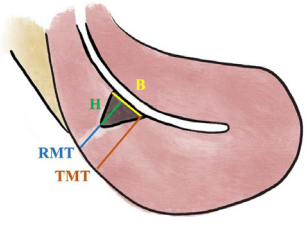
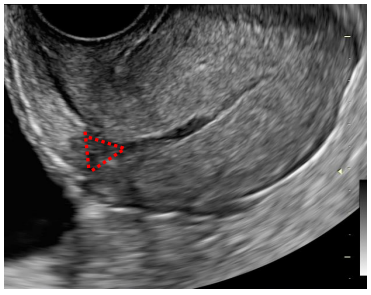
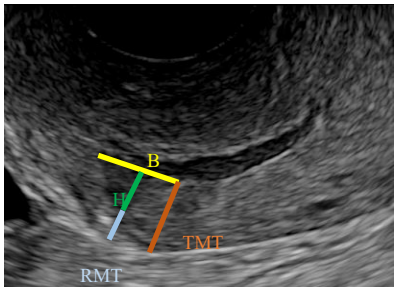


Fig. 2. Uterine niche measurements. The following measurements were performed: B = the scar base, H = niche height, RMT = residual myometrial thickness, and TMT = total myometrial thickness.



3a



3b

Fig. 3. Transvaginal ultrasonography. (a) A triangular niche formed at the uterine incision (denoted by the dotted line). (b) Measurement parameters.
B = base of the scar, H= height of the scar, RMT= residual myometrial thickness, TMT= total myometrial thickness.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 27; SPSS Inc., Chicago, IL, USA). Differences in ultrasonographic findings were calculated using the chi-square, Fisher's exact, and independent t-tests, as appropriate. The effects of factors associated with a large CSD were adjusted using multiple logistic regressions. Statistical significance was set at $p < 0.05$.

Results

A total of 94 participants provided informed consent to participate in the study. The baseline characteristics and demographic data are presented in Table 1. The majority (68.1%) of participants had primary CS, in which the indications for emergency CS were cephalopelvic disproportion (CPD), failed induction, abnormal fetal presentation, and abnormal fetal tracing. CPD was the highest in the primary emergency CS group (47.1 %). Thirteen participants underwent elective primary CS due to abnormal fetal presentations (38.5%), fetal macrosomia (7.7%), and maternal requests (53.8%). Labor was not augmented or induced with oxytocin in any patient in the repeated CS group. No participant had a cervical dilatation of ≥ 6 cm at the time of CS in the repeated CS group. All the women in the repeated CS group were scheduled for an elective CS. If labor commenced before the scheduled date, they underwent emergency CS. Cervical dilatation of 6 cm was chosen because it is the cut-off value for active labor[14]. The operative time in the primary CS population (54.8 ± 12.8 minutes) was shorter than that in the repeated CS population (70.5 ± 21.0 minutes).

Ultrasound findings of women with primary CS and repeated CS at six weeks after surgery are shown in Table 2. We observed 57 participants with anteflexed uteri and 37 with retroflexed uteri. The mean height and base in the repeated CS group (7.53 mm and 8.43 mm, respectively), were higher than those of the primary CS group (4.63 mm and 6.05 mm, respectively) ($p < 0.001$). The mean TMT in the primary and repeated CS groups was 13.24 mm and 15.21 mm, respectively ($p = 0.01$). The TMT in the primary CS group was lower because 13 of the 64 (20.0%) women had advanced labor. The mean RMT in the primary CS group (8.16 mm) was higher than that in the repeated CS group (5.42 mm) ($p < 0.001$). Large CSDs were detected in 10 (15.6%) and 11 (36.7%) women in the primary and repeated CS groups ($p = 0.02$). The overall prevalence of large CSD was 22.3%. A total of three (4.7%) and five (16.7%) patients in the primary and repeated CS groups were found to have thin RMTs ($p = 0.05$). The factors associated with large CSDs are shown in Table 3 and include the number of CS ($p = 0.002$), cervical dilatation ≥ 6 cm at the time of CS ($p = 0.023$),

and uterine retroflexion (p = 0.015). These factors had a statistically significant relationship to large CSDs. Repeated CS, cervical dilatation ≥ 6 cm at the time of CS, and uterine retroflexion showed 8.85 (95% confidence interval (CI) 2.29-34.15), 5.84 (95%CI 1.28-26.71), and 4.40 (95%CI 1.33-14.55) odds of a person developing a large CSD, respectively.

Table 1. Baseline characteristics (total n = 94).

Parameters	Primary CS (n = 64)	Repeated CS (n = 30)
Age*	29.2 ± 6.0	33.8 ± 4.8
Age < 35 years	52 (81.2%)	14 (46.7%)
Age ≥ 35 years	12 (18.8%)	16 (53.3%)
Pre-pregnancy BMI*	24.7 ± 4.7	23.6 ± 7.0
BMI < 25 kg/m^2	41 (64.1%)	19 (63.3%)
BMI ≥ 25 kg/m^2	23 (35.9%)	11 (36.7%)
Gestational age at delivery (weeks)*	38.6 ± 1.0	38.4 ± 0.9
Pregestational diabetes	1 (1.6%)	0
Gestational diabetes	16 (25.0%)	6 (20.0%)
Maternal anemia (Hb < 11 g/dL)	6 (9.4%)	4 (13.3%)
Emergency Cesarean	51 (79.7%)	15 (50.0%)
Oxytocin use during labor	30 (46.9%)	0
Cervical dilatation at the time of decision for CS		
< 6 cm	51 (79.7%)	30 (100.0%)
≥ 6 cm	13 (20.3%)	0
Operator		
Attending physician	15 (23.4%)	9 (30.0%)
Resident	49 (76.6%)	21(70.0%)
Operative time (minutes)*	54.8 ± 12.8	70.5 ± 21.0
Postpartum hemorrhage (> 1,000 mL)	9 (14.1%)	1 (3.3%)

* mean ± standard deviation
CS: cesarean section, BMI: body mass index, Hb: hemoglobin

Table 2. Ultrasound findings of the patients (total n = 94).

Findings	Primary CS (n = 64)	Repeated CS (n = 30)	p value
Uterine position			
Anteflex	34	23	0.030*
Retroflex	30	7	
Scar defect parameters			
Height (mean ± SD, mm)	4.63 ± 2.20	15 ± 3.26	< 0.001**
Base (mean ± SD, mm)	6.05 ± 1.84	8.43 ± 3.26	
Myometrial thickness			
TMT (mean ± SD, mm)	13.24 ± 3.31	15.21 ± 3.82	0.010**
RMT (mean ± SD, mm)	8.16 ± 3.40	5.42 ± 2.40	
Number of large scar defects	10	11	0.020*
Number of thin RMT	3	5	0.050***

* Chi-square test, **Independent t-test, ***Fisher's exact test
CS: cesarean section, SD: standard deviation, RMT: residual myometrial thickness, TMT: total myometrial thickness
Thin RMT is defined as myometrial thickness ≤ 3 mm.

Table 3. Factors that correlate with large Cesarean scar defect.

Parameters	Crude Odds	95%CI	p value	Adjusted OR*	95%CI	p value
Repeated CS	3.14	1.15 - 8.53	0.026	8.85	2.29 - 34.15	0.002
Cervical dilatation ≥ 6 cm	2.54	0.73 - 8.81	0.142	5.84	1.28 - 26.71	0.023
Uterine retroflexion	2.56	0.95 - 6.89	0.063	4.40	1.33 - 14.55	0.015

* Adjusted for uterine version, age, body mass index (obesity), maternal diabetes (pregestational diabetes and gestational diabetes), urgency, postpartum hemorrhage, surgeon, cervical dilatation, oxytocin use during labor, gestational age, repeat or primary CS, and total operative time.
CI: confidence interval, OR: odds ratio, CS: cesarean section

Discussion

The prevalence of large CSD was 22.3% at six weeks postpartum in our study. It was 15.6% in the primary CS group and 36.7% in the repeat CS group. Multivariate analysis demonstrated that repeated CS, uterine retroflexion, and cervical dilatation ≥ 6 cm at the time of CS were associated with large CSDs.

Our study verified that patients with repeated CS had higher odds ratio of developing a large CSD. Repeated CS has been reported to result in prominent CSDs; however, the measurements were performed 3 months postpartum or even later[13, 15, 16]. Our findings at 6 weeks postpartum were consistent with those of previous studies. Repetitive trauma favors the development of scarred tissue, chronic inflammation, altered cytokines, and poor vascularization[11, 17]. A compromised healing cascade results in the discontinuation of the myometrial tissue, leading to a large CSD. Moreover, in repeated CS, the epithelized ends of the scarred myometrium are difficult to recognize. This results in incomplete repair of the myometrial tissue, favoring the development of a large CSD[18].

The scar maturation process at the incision site post-CS starts at approximately 3 months. The complete anatomical involution of the uterus takes approximately six months[19]. At 6 weeks, intrauterine fluid is still present, which could assist in CSD visualization. Owing to the considerable uterine involution, performing ultrasonography after 3-6 months usually requires gel or normal saline instillation. We performed non-instillation ultrasonography at six weeks postpartum to adequately locate and identify large CSDs. This early detection of large CSDs may impact patient medical care and future fertility planning. However, there is no standardized optimal timing for postpartum CSD evaluation.

Previous studies have measured uterine defects at 3, 6, or 12 months postpartum[12, 15, 20]. At 6 weeks postpartum, the uterus has not fully involute, and scar healing at the uterotomy incision is still in progress. Gull et al reported that CSD presence does not change from 6 weeks to 1 year; however, the scar shape may change owing to maturation[9]. A study from Taiwan compared post-CS uterine scars and myometrial thickness at 6 weeks and 6 months; no difference in the scar dehiscence risk or significant changes in the myometrial thickness were found. Therefore, CSD can be evaluated as early as six weeks[21].

We used 2D ultrasonography for CSD measurements in this study, as per current consensus[12, 22]. One study compared 2D and three-dimensional (3D) ultrasonography for CSD evaluation and found comparable results[23]. 3D ultrasonography is considered a promising tool for visualizing CSD as it can evaluate its volume and shape[24]. Further studies are required to demonstrate the superiority of 3D ultrasound over 2D ultrasound in CSD measurements.

In our study, uterine retroflexion was correlated with a large CSD. During retroflexion, the uterus is under tension. If the abdominal wall has adhesions, the counteracting force becomes more prominent. This tension disrupts healing at the hysterotomy site. Furthermore, the lower segment of the retroflexed uterus is more stretched and less perfused[13]. This

uterine habitus is a result of genetic build or pelvic pathology, such as pelvic adhesions caused by a previous surgery.

We found that performing CS in women with cervical dilatation ≥ 6 cm increased the risks of large CSDs. During advanced labor, there is stretching and thinning of the lower uterine segment. The uterus is repaired without including all the myometrium as the approximation of underlying muscles is incomplete. This leads to myometrial retraction at the scar site, ultimately resulting in a large CSD[18].

The major strengths of this study were the ability to detect large CSDs early and confirmed their association with repeated CS. To our knowledge, this is the first study to verify that more than one CS was associated with a large CSD at six weeks postpartum. The findings of this study could ultimately prevent adverse consequences, especially in patients of childbearing age. Additionally, we employed a single sonographer. Therefore, there were no inter-observer variations in the measurements.

This study had some limitations. The scar defects were assessed at a single point in time. Follow-up measurements to observe scar maturation would be beneficial. Since the scar measurements were performed only once, intra-observer agreement was not calculated. We performed a non-instillation ultrasound, which may not allow a comprehensive depiction of the scar morphology compared to a gel or normal saline instillation ultrasound. Moreover, our institution does not provide vaginal birth after cesarean delivery, and participants with advanced cervical dilatation, which was significantly associated with large CSDs, were all in the primary CS group.

Our study findings have several clinical applications. The study results could enhance treatment strategies and prevent CSD-related complications. Recognizing the condition as early as six weeks postpartum allows safer shared-care decisions between the patient and physician. The treatment strategies may include fertility planning, preconception counseling, and appointments for CSD follow-up. Therefore, CSD detection combined with proper treatment can improve the patient's quality of life.

In the future, transvaginal ultrasonography may be considered during postpartum visits in high-risk groups, such as patients with repeated CS and those who underwent CS during advanced labor. Patients with large CSDs could be offered close follow-up and treated as necessary. Those planning for future pregnancies should be advised for preconception care, followed by an early first-trimester scan to ensure normal intrauterine pregnancy. Currently, there is no definite protocol for CSD monitoring post-CS and in patients with large CSDs. We hope to be part of the new medical care guidelines that would focus on such patients.

We also hope to follow-up postpartum patients for a longer time, to obtain a complete picture of CSD progression. Estimation of inflammatory markers at the CSD site could also be performed to confirm the altered environment and ultimately help develop appropriate treatment protocols.

Conclusion

The prevalence of large CSDs at six weeks postpartum was higher in patients with repeated CS, uterine retroflexion, and cervical dilatation ≥ 6 cm at the time of CS.

Acknowledgments

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Prevalence of Appendiceal Pathology in Ovarian Cancer When Appendectomy is performed during Surgical Treatment

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ABSTRACT

Objectives: Pathological appendectomy findings during the surgical staging procedure for ovarian cancer can determine the extent of the cancer, and specific treatment depends on whether a primary appendiceal malignancy or an ovarian metastasis is involved. This study aimed to evaluate appendiceal histology from comprehensive surgery for epithelium ovarian cancer.

Materials and Methods: We retrospectively evaluated patients who underwent cytoreductive surgery for primary and secondary epithelium ovarian cancer and who had undergone an appendectomy between 2003 and 2016. The clinicopathologic findings concerning ovarian cancer and the appendix, and risk factors for appendiceal abnormalities were presented.

Results: Of 340 patients with ovarian cancers, 322 (94.7%) were diagnosed with primary epithelium ovarian cancer and 60.6% were at an early stage. Mucinous carcinoma was the most common in histology (40%). Appendiceal malignancies were identified in 53 (15.6%) patients, of whom 42 (12.4%) had secondary metastasis from ovarian cancer, and two patients had stomach or breast metastases. Primary appendiceal neoplasms were identified in nine patients, with three patients presenting with synchronous ovarian cancers. A grossly abnormal appendix (odds ratio [OR] 27.6, 95% confidence interval [CI] 7.1–107.3, $p < 0.001$), advanced stage ovarian cancer (OR 114.6, 95%CI 14.6-99.4, $p < 0.001$), and secondary ovarian cancer (OR 86.7, 95%CI 8.5-887.7, $p < 0.001$) were associated with appendiceal neoplasm in multiple logistic regression analysis.

Conclusion: Appendiceal neoplasm accompanied a significant number of ovarian cancers. Appendectomy is recommended as part of surgical staging in abnormal looking appendices, advanced ovarian cancer, and secondary ovarian cancer.

Keywords: appendectomy, appendix, ovarian cancer, pathology.

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พยาธิสภาพของไส้ติ่งในผู้ป่วยมะเร็งเยื่อบุผิวรังไข่ที่ได้รับการตัดไส้ติ่งในขณะผ่าตัดมะเร็งรังไข่

อรุณธร พิเชฐชัยยุทธ์, รักชาย บุหงาชาติ, กรัณฑรัตน์ ปิยนันท์จรัสศรี, ศรันญา วัฒนกำธรกุล, ยุทธศักดิ์ ศุภสินธุ์, สาธนา บุณยพิพัฒน์, คณิตา กายะสุต, อดิศร ชัยกิจ

บทคัดย่อ

วัตถุประสงค์: *พยาธิวิทยาของไส้ติ่งที่ได้จากการตัดไส้ติ่งในระหว่างการผ่าตัดรักษามะเร็งเยื่อบุผิวรังไข่สามารถระบุความกว้างไกลของการแพร่กระจายของมะเร็งรังไข่ได้ ซึ่งการรักษาเพิ่มเติมก็ขึ้นกับว่ามะเร็งที่อยู่ที่ไส้ติ่งนั้นเป็นมะเร็งปฐมภูมิที่ไส้ติ่งเองหรือเกิดจากการแพร่กระจายมาจากมะเร็งเยื่อบุผิวรังไข่ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินผลทางพยาธิวิทยาของไส้ติ่งที่ได้จากการผ่าตัดรักษามะเร็งรังไข่ชนิดเยื่อบุผิว*

วัสดุและวิธีการ: *เป็นการศึกษาจากข้อมูลย้อนหลังในผู้ป่วยที่ได้รับการผ่าตัดรักษามะเร็งรังไข่ชนิดเยื่อบุผิวหรือลุกลามมาจากมะเร็งของอวัยวะอื่นของร่างกาย ร่วมกับการผ่าตัดไส้ติ่งในระหว่างปีพุทธศักราชที่ 2546 ถึง 2559 เพื่อนำข้อมูลมาประเมินลักษณะทางพยาธิวิทยาและปัจจัยเสี่ยงที่นำไปสู่ความผิดปกติของไส้ติ่ง*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ในการศึกษาครั้งนี้มีจำนวน 340 ราย พบว่า 322 รายเป็นมะเร็งรังไข่เยื่อบุผิวชนิดปฐมภูมิคิดเป็นร้อยละ 94.7 และร้อยละ 60.6 อยู่ในระยะแรก มิวซินัสคาร์ซิโนมาเป็นมะเร็งที่พบบ่อยที่สุดถึงร้อยละ 40 มะเร็งที่ไส้ติ่งพบในผู้ป่วยทั้งหมด 53 รายคิดเป็นร้อยละ 15.6 ของผู้ป่วยทั้งหมด โดยมีอยู่ 42 รายหรือร้อยละ 12.4 เกิดจากการแพร่กระจายมาจากมะเร็งรังไข่ และผู้ป่วยอีก 2 รายมีการแพร่กระจายมาจากกระเพาะอาหารและเต้านม ส่วนมะเร็งปฐมภูมิของไส้ติ่งพบได้ 9 ราย ในจำนวนเก้ารายนี้ มีอยู่ 3 สามรายที่พบว่าเป็นมะเร็งปฐมภูมิถึงสองชนิดคือมะเร็งไส้ติ่งเองและมะเร็งเยื่อบุผิวรังไข่ร่วมด้วย ปัจจัยที่มีผลต่อลักษณะทางพยาธิวิทยาของไส้ติ่งจากการวิเคราะห์ถดถอยโลจิสติกได้แก่ ลักษณะทางกายภาพของไส้ติ่งที่ผิดปกติขณะผ่าตัด (odds ratio 27.6, 95% confident interval 7.1–107.3, $p < 0.001$) มะเร็งรังไข่ที่พบมีการลุกลามออกนอกรังไข่ (odds ratio 114.6, 95% confident interval 14.6-99.4, $p < 0.001$) และมะเร็งรังไข่ชนิดทุติยภูมิ (odds ratio 86.7, 95% confident interval 8.5-887.7, $p < 0.001$)*

สรุป: *ขณะทำการผ่าตัดรักษามะเร็งของรังไข่สามารถพบมะเร็งที่ไส้ติ่งร่วมด้วยได้ ทางคณะผู้วิจัยจึงแนะนำให้มีการผนวกการตัดไส้ติ่งเป็นส่วนหนึ่งของขั้นตอนการผ่าตัดรักษามะเร็งรังไข่ด้วยในผู้ป่วยที่ไส้ติ่งดูผิดปกติขณะผ่าตัดช่องท้อง ในมะเร็งรังไข่ระยะลุกลาม และในมะเร็งรังไข่ชนิดทุติยภูมิ*

คำสำคัญ: *ตัดไส้ติ่ง, ไส้ติ่ง, มะเร็งรังไข่, พยาธิวิทยา*

Introduction

Recommendations for routine appendectomy in the management of ovarian cancer remain unclear. International Federation of Gynecology and Obstetrics (FIGO) Committee[1] and National Comprehensive Cancer Network[2] guidelines recommend routine appendectomy for mucinous ovarian cancer to differentiate between primary ovarian origin and secondary metastasis from the appendix, and also as part of cytoreductive surgery for optimal tumor debulking. Some studies have reported a significant rate of upstaging in early-stage disease owing to isolated occult appendiceal metastasis and a high rate of appendiceal metastasis in the advanced stage[3-5]. However, other studies have not recommended routine appendectomy because of a low rate of appendiceal involvement in early-stage disease[6, 7]. This study aimed to evaluate the prevalence of appendiceal pathology in patients undergoing surgical staging and selected appendectomy to treat ovarian cancer and identify factors that increase its risk.

Materials and Methods

This retrospective study was conducted in Songklanagarind Hospital, a tertiary referral center in southern Thailand. This study was approved by the Human Ethics Committee of the Faculty of Medicine, Prince of Songkhla University. The requirement for informed consent was waived given the anonymity of the routine data. We reviewed the medical records of patients diagnosed with ovarian cancer classified according to the FIGO staging system[2, 8, 9] between 2003 and 2016. The inclusion criteria were: 1) patients with primary epithelial and secondary ovarian cancer, 2) who had undergone primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon. The histological types of primary epithelial and secondary ovarian cancer were classified according to the World Health Organization classification[2, 8]. All pathologic slides were reviewed by the pathologist in our study. The exclusion criteria were 1) patients who had a sex cord-stromal tumor or germ cell tumor, 2) who underwent prior appendectomy, 3) who did not have an appendix pathological report and 4) incomplete data.

The sample size was calculated based on a 37% appendiceal metastasis rate in ovarian carcinoma[3], indicating that a total of 335 patients would be necessary for the analysis. Appendiceal pathology was defined according to the World Health Organization classification of tumors of the appendix[10]. The definition of coexisting ovarian and appendiceal tumors or synchronous primary tumors was established according to morphology, pattern of tumor spreading, immunohistochemistry, and genetic analysis[11-13]. A grossly abnormal appendix was considered to involve mucocele, thickening of the appendiceal wall, adhesions, tumor implants, nodules, mass, swelling, hyperemia, and distension, which were examined through visual inspection and palpation. Statistical analysis was performed using Statistical Package for the Social Science version 17 package program (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as median and range. Categorical variables were presented as counts and percentages. Patient characteristics were analyzed by student t-test for continuous variables and Chi-squared test for categorical variables. Univariate and multivariate analyses were performed. P values less than 0.05 were considered statistically significant.

Results

Patient and clinicopathological characteristics

Among the 1716 ovarian cancer patients at the time period, 340 patients were included and their clinicopathological characteristics are shown in Table 1. The most common histological type was mucinous tumor. Most patients had been diagnosed with primary epithelial ovarian cancer and 18 (5.3%) had been diagnosed with secondary ovarian cancer. Of 322 patients with primary epithelial ovarian cancer, most (43.5%) had stage I disease. Of 340 patients, 332 (97.7%) had undergone radical surgery, and eight (2.3%) patients with early-stage disease had undergone conservative surgery.

Table 1. Clinicopathological characteristic of the patients.

Characteristics (n = 340)	n (%)
Age (years), median (range)	50 (12–85)
FIGO stage	
Stage I-II	206 (60.6)
Stage III-IV	116 (34.1)
Metastases secondary to:	
Colorectal cancer	6 (1.8)
Appendix	6 (1.8)
Stomach	4 (1.1)
Breast	1 (0.3)
Thyroid	1 (0.3)
Histology	
Mucinous	136 (40.0)
Serous	76 (22.4)
Endometrioid	46 (13.5)
Clear cell	42 (12.4)
Adenocarcinoma	28 (8.2)
Mixed type	12 (3.5)
Ascites	
Mucin	27 (8.0)
Non-mucin	183 (53.8)
Cytology Positive	65 (19.1)
Tumor diameter (cm), median (range)	15 (2–60)
Tumor side: Bilateral	80 (23.5)
Peritoneal seeding	65 (19.1)
Presence of extraovarian tumor	178 (52.4)
Gross appearance of appendix Abnormal	29 (8.5)
Diameter of appendix (cm), median (range)	0.6 (0.5–6)
Length of appendix (cm), median (range)	5.0 (0.5–9)
Ovarian tumor	
Intact	190 (55.9)
Incidental rupture during operation	84 (24.7)
Previous rupture	59 (17.4)

Prevalence of appendiceal pathology in ovarian cancer

Of 340 patients, 53 (15.6%) had appendiceal pathology findings, including six (1.8%) with primary appendiceal cancer, three (0.9%) with coexisting or synchronous ovarian and appendiceal tumors, 42 (12.4%) with secondary appendiceal cancers that had metastasized from the ovary, and one with secondary appendiceal metastasis from the stomach and one from the breast. The clinical characteristics of the nine patients with primary appendiceal cancer and coexisting or synchronous appendiceal and ovarian tumors are shown in Table 2. Of six patients with primary appendiceal cancer, the gross appearance of the appendix was normal in two patients. Of three patients with synchronous appendiceal and ovarian tumors, one patient had a normal appendix.

Of 340 patients, 29 (8.5%) had a grossly

abnormal appendix, of whom 23 (79.3%) had abnormal histology findings. Of 311 patients with a healthy appearing appendix, 30 (9.6%) had appendiceal pathology.

Of 136 patients with ovarian cancer and a mucinous cell subtype, 11 (8.1%) had appendiceal pathology, which comprised primary mucinous appendiceal cystadenocarcinoma with metastasis to the ovary in five patients and secondary metastasis from ovarian cancer in six patients.

Table 2. Clinicopathological characteristics of patients with primary appendiceal tumors and synchronous ovarian and appendiceal tumors.

Patient	Age (years)	Ovary histology	Ovarian tumor status	Largest size of ovarian tumor (cm)	Ascites	Gross appearance of appendix intraoperatively	Tumor biochemical markers	Appendix histology
1	68	Mixed endometrioid and clear cell	Previous rupture	20	Straw color ascites 500 ml	Swelling	Not performed	Well-differentiated neuroendocrine tumor (carcinoid)
2	72	Serous cystadenocarcinoma	No rupture	10	None	Normal	Not performed	Mucinous cystadenoma
3	60	Clear cell	Accidental rupture	20	Straw color ascites 2400 ml	Mucocele	Not performed	Low grade mucinous cystadenocarcinoma
4	52	Metastasis from appendix	Previous rupture	25	Pseudomyxoma peritonei	Swelling	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
5	77	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Mucocele	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
6	50	Metastasis from appendix	Previous rupture	30	Pseudomyxoma peritonei	Mucocele	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
7	68	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Normal	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
8	34	Metastasis from appendix	Previous rupture	20	Serosanguinous ascites 200 ml	Phlegmon	CK20 positive CK7 negative	Primary adenocarcinoma
9	73	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Normal	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma

CK: cytokeratin

Prevalence of appendiceal pathology in primary epithelial ovarian cancer

Of 322 patients with primary epithelial and secondary ovarian cancer who had undergone primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon, 45 patients had appendiceal pathology, of whom 42 (13.0%) patients had secondary appendiceal metastasis from ovarian cancer, one had a carcinoid tumor, one had a primary appendiceal mucinous cystadenoma, and one had a primary appendiceal low grade mucinous cystadenocarcinoma.

Of 206 patients with early stage (I-II) epithelial ovarian cancer, one patient had a coexisting carcinoid appendiceal tumor. The rate of appendiceal metastasis from primary epithelial ovarian cancer was 36.2% (42 of 116 patients) in advanced-stage disease (III-IV) and none in early-stage disease.

Factors associated with appendiceal pathology

Of 340 patients, 53 had appendiceal pathology and 287 had a normal appendix histology. Potential factors associated with appendiceal pathology are shown in Table 3. In the multiple logistic regression analysis (Table 4) after being adjusted by the significant variables ($p<0.05$) from univariate analysis, appendiceal pathology was found to be significantly associated with the presence of a grossly abnormal appendix, advanced-stage disease of primary epithelial ovarian cancer, and secondary ovarian cancer.

Table 3. Univariate analysis of factors associated with appendiceal pathology.

Variable	Appendiceal pathology (n=53) n (%)	No appendiceal pathology (n=287) n (%)	OR (95% CI)	p value
Age (years)				
≤ 45	13 (11.8)	97 (88.2)	1	0.2
> 45	40 (17.4)	190 (82.6)	1.6 (0.8–3.1)	
FIGO Stage				
Stage I-II	1 (0.5)	205 (99.5)	1	<0.001
Stage III-IV	44 (37.9)	72 (62.1)	125.3 (16.9–925.8)	
Metastasis	8 (44.4)	10 (55.6)	164.0 (18.6–1441.5)	
Histology				
Mucinous	11(8.1)	125 (91.9)	1	<0.001
Serous	24 (31.6)	52 (68.4)	5.2 (2.4–11.4)	
Others	18 (14.1)	110 (85.9)	1.9 (0.8–4.1)	
Ascites				
Absent or non-mucin	47 (15.0)	266 (85.0)	1	0.3
Mucin	6 (22.2)	21 (77.8)	1.6 (0.6–4.2)	
Cytology				
Negative	20 (9.5)	191(90.5)	1	<0.001
Positive	17 (26.2)	48 (73.8)	3.4 (1.6–6.9)	
No data	16 (25.0)	48 (75.0)	-	
Tumor side				<0.001
Left side	12 (10.0)	108 (90.0)	1	
Right side	12 (8.6)	128 (91.4)	0.8 (0.3–1.9)	
Bilateral	29 (36.3)	51 (63.7)	5.1 (2.4–10.8)	
Tumor diameter (cm)				
≤10	18 (19.6)	74 (80.4)	1	0.2
>10	32 (14.2)	194 (85.8)	0.7 (0.3–1.2)	
No data	3 (13.6)	19 (86.4)	-	
Peritoneal seeding				
No seeding	25 (9.1)	250 (90.9)	1	<0.001
Seeding	28 (43.1)	37 (56.9)	7.6 (3.9–14.4)	
Extraovarian tumor				
No	7 (4.3)	155 (95.7)	1	<0.001
Yes	46 (25.8)	132 (74.2)	7.7 (3.4–17.6)	
Gross of appendix				
Normal	30 (9.6)	281 (90.4)	1	<0.001
Abnormal	23 (79.3)	6 (20.7)	35.9 (13.5–95.1)	
Diameter of appendix (cm)				
< 1	32 (12.3)	229 (87.7)	1	<0.001
≥ 1	19 (45.2)	23 (54.8)	5.9 (2.9–12.0)	
No data	2 (5.4)	35 (94.6)	-	
Ovarian tumor				
Intact or incidental rupture	39 (14.2)	235 (85.8)	1	0.1
Previous rupture	13 (22.0)	46 (78.0)	1.7 (0.8–3.4)	
No data	1 (14.3)	6 (85.7)	-	

CI: confidence interval, OR: odds ratio

Table 4. Multiple logistic regression analysis of factors associated with appendiceal pathology.

Variables	Adjusted OR (95% CI)	p value
FIGO stage		
Stage I-II	1	<0.001
Stage III-IV	114.6 (14.6–901.4)	
Metastasis	86.7 (8.5–887.7)	
Gross appearance of appendix		
Normal	1	<0.001
Abnormal	27.6 (7.1–107.3)	

Adjusted for age, histology, cytology, status of ovarian capsule, peritoneal seeding, and extraovarian tumor.
CI: confidence interval, OR: odds ratio

Prevalence of appendectomy associated complications

One patient had a suspected bowel perforation two weeks after an operation for stage IIIC mucinous cystadenocarcinoma. The second operation revealed an acute suppurative inflammation.

Discussion

This retrospective study evaluated the prevalence of appendiceal pathology in ovarian cancer patients undergoing primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon and also determined factors that increased its risk. In this study, the overall prevalence of appendiceal pathology in ovarian cancer was 15.6%, comprising 12.4% (42 of 340) of patients with secondary appendiceal metastasis from ovarian cancer and 2.6% (9 of 340) of patients with primary appendiceal cancer and coexisting ovarian and appendiceal tumors. The actual rate of primary appendiceal cancer and coexisting appendiceal and ovarian tumors during surgical treatment for ovarian cancer is unknown. However, Timofeev et al[14] reported that the prevalence of primary appendiceal cancers diagnosed during surgical exploration for a pelvic mass was 10.5% (20 of 191 study patients), and Wong et al[15] reported the prevalence of primary appendiceal cancer to be 4.2% in 9 of 213 patients in their study.

Regarding the gross appearance of the appendix, the rate of appendiceal pathology in a grossly abnormal appendix was 79.3%, which was relatively high compared to the findings of Timofeev et al[14]. This result supports our general practice, which advocates appendectomy in cases of an abnormal gross appearance of the appendix.

Regarding the mucinous histological subtype of ovarian tumors, appendectomy is recommended to distinguish the primary appendiceal origin. In this study, the rate of appendiceal pathology from a total of 136 patients with ovarian cancer of a mucinous cell subtype was 8.1%. These findings are similar to the results of a meta-analysis by Cheng et al[16], which included a total of 353 patients with mucinous ovarian cancer who underwent appendectomy; they estimated the rate of appendiceal pathology to be 6.3% and as high as 59% for patients with an abnormal gross appearance of the appendix. Feigenberg et al[17] studied a total of 77 patients with mucinous adenocarcinoma and mucinous borderline tumor; among them, 11 patients (14%) were diagnosed with primary appendiceal carcinoma with metastasis to the ovary and none had secondary appendiceal metastasis from the ovary. Of those 11 patients, 72.7% (8/11) had a grossly abnormal appendix. They concluded that there was insufficient evidence to support routine appendectomy in patients with a normal gross appearance of the appendix[16, 17].

The prevalence of appendiceal metastasis in primary epithelial ovarian cancer was found to be 13.0% in this study. Most appendiceal metastasis (36.2%, [42/116]) occurred in advanced-stage disease, whereas none occurred in the early stage, which was comparable to findings reported in several

other studies[3, 5-7, 14, 18]. Most studies have reported a high rate of appendiceal involvement in patients with a serous cell subtype and advanced-stage disease[3, 5, 14, 18]. A high prevalence of appendiceal metastasis in advanced-stage disease (42.2-71.8%)[3, 5, 14, 18] has also been reported in contrast to a very low rate in early-stage disease[3, 5-7, 14, 18].

Considering the outcomes of microscopic appendiceal metastasis, 8.4% (26/311) of patients whose appendix appeared to be normal had occult metastasis from the ovary. Of 26 patients, 25 had stage III-IV disease, and all these patients had other evidence of advanced-stage disease. Therefore, additional appendectomy did not alter the final stage but could have been beneficial for optimal cytoreductive surgery.

In this study, factors significantly associated with appendiceal pathology included advanced-stage disease of primary epithelial ovarian cancer, secondary ovarian cancer, and a grossly abnormal appearance of the appendix. Previous studies have reported a higher rate of appendiceal metastasis in patients with advanced-stage disease[3, 5] and a grossly abnormal appendix[14]. In contrast, Kokanali et al[18] reported tumor grade, the presence of ascites, the right side of the tumor, and large tumor size (>10 cm) as factors that significantly increased the risk of appendiceal metastasis, which were not found to be significant factors in our study. Performing a comprehensive exploration intraoperatively at the time of surgical treatment for ovarian cancer is important as is a careful evaluation of the appendix and removal of all suspected abnormal diseased tissue. Most studies[3, 5] recommend routine appendectomy; however, an appendectomy is not without risk, and complications such as intraabdominal abscess, intestinal obstruction, bowel perforation, and stump leakage can occur.

Al-Temimi et al[19] reported that incidental appendectomy increased the risk of morbidity in patients undergoing elective surgery (odds ratio (OR) 1.31, 95% confidence interval (CI) 1.03-1.68), and that it was also associated with an increased risk of postoperative wound complications (OR 1.46, 95% CI 1.05-2.03). In our study, one patient was diagnosed with appendiceal site perforation two weeks after primary surgery, and the rate of appendectomy associated complications was 0.3% (1/340).

In spite of the significant number of appendiceal pathologies in ovarian cancer of our study, this is limited by a retrospective in design and might have some missing data. In addition, the details of clinical treatment and data varied across the study. Even the treatments followed the guideline of the institute but were done by many surgeons. The decision of whether to remove the appendix intraoperatively remains individual and there is bias. The differing incidence of a more proportion of mucinous cancer than previous studies, as well as the different distribution of ovarian cancer subtypes, should be further explored, as these may provide insight into the mechanisms of ovarian carcinogenesis.

Conclusion

In conclusion, the study has shown that there is a potential for appendiceal pathology in patients who are presented with a grossly abnormal appendix, secondary ovarian cancer, or advanced-stage (III-IV) primary epithelial ovarian cancer. The distribution of appendiceal histology and the origin of the cancer prompts surgeons to consider appendectomy as part of surgical staging in relation to ovarian cancer clinical practice.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Treatments and Outcomes of Epithelial Ovarian Cancers in Srinagarind Hospital

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ABSTRACT

Objectives: To compare treatments of epithelial ovarian cancers (including fallopian tube cancer and primary peritoneal adenocarcinoma) with national guidelines and oncological outcomes between standard and non-standard treatment groups.

Materials and Methods: Retrospective chart reviews were performed on patients with epithelial ovarian cancers, fallopian tube cancer and primary peritoneal adenocarcinoma (n = 318) who had been registered in Department Obstetrics and Gynecology, Srinagarind Hospital, between January 1st, 2014 and December 31st, 2019. Surgical treatments and adjuvant treatments were compared with national guidelines. Oncological outcomes were compared between standard and non-standard treatment groups. Univariate and multivariate logistic regression analyses were used for factors to receive which treatment. Survival rates were analyzed by Kaplan-Meier and prognostic factors were compared among the two groups by Cox-regression for factors to receive longer overall survival.

Results: A total of 318 patients were recruited. Most patients were diagnosed with epithelial ovarian cancers (89.9%). The major pathology was high grade carcinoma (53.8%). Surgeries were done in most patients (92.1%), which were primary cytoreductive surgery (72.4%) and complete surgical staging (80.5%). Residual tumors of more than 5 mm in diameter were left in 42.3%. Standard and non-standard treatment of epithelial ovarian cancers were found in 60.4% (95% confidence interval: 54.9-65.6%) and 39.6%, respectively. Chemotherapies were given to most patients (86.8%). Five-year survival rates and recurrence free survival rates were 42.2% and 26.8%. Overall survival rate was significantly lower in the non-standard group (adjusted hazard ratio = 1.42, 95% confidence interval: 1.01-2.02, p = 0.046).

Conclusion: National guidelines on treatment of epithelial ovarian cancers should be followed, because of poorer outcomes in the non-standard groups.

Keywords: treatments, oncological outcomes, epithelial ovarian cancers, national guideline recommended therapy.

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วิธีและผลการรักษาของโรคมะเร็งเยื่อบุผิวรังไข่ในโรงพยาบาลศรีนครินทร์

จิรภิญญา ชุมวรฐายี, บัณฑิต ชุมวรฐายี, สงวนโชค ล้วนรัตนากร, อมรรัตน์ เต็มธนะกิจไพศาล, นราทัศพล ลิขิตดี, ยุวดี อิฐรัตน์

บทคัดย่อ

วัตถุประสงค์*: เพื่อเปรียบเทียบวิธีการรักษามะเร็งเยื่อบุผิวรังไข่ (รวมถึงมะเร็งท่อนำไข่และมะเร็งเยื่อบุช่องท้องปฐมภูมิ) กับแนวทางการรักษามาตรฐาน และผลการรักษามะเร็งเหล่านี้ ระหว่างกลุ่มที่ได้รับวิธีการรักษามาตรฐานกับวิธีการรักษาที่มิใช่มาตรฐาน*

วัสดุและวิธีการ*: ทบทวนและเก็บข้อมูลจากที่มีบันทึกอยู่ ในเวชระเบียนของผู้ป่วยที่ได้รับการวินิจฉัย ว่าเป็นมะเร็งเยื่อบุผิวรังไข่ มะเร็งท่อนำไข่และมะเร็งเยื่อบุช่องท้องปฐมภูมิ (n = 318) ในสาขาวิชาสูติศาสตร์และนรีเวชวิทยา โรงพยาบาลศรีนครินทร์ ระหว่างวันที่ 1 มกราคม 2557 ถึงวันที่ 31 ธันวาคม 2561 เปรียบเทียบวิธีการรักษาด้วยการผ่าตัดและการรักษาเสริมด้วยยาเคมีบำบัดกับแนวทางการรักษามาตรฐาน และเปรียบเทียบผลการรักษามะเร็งระหว่างกลุ่มที่ได้รับวิธีการรักษามาตรฐานกับวิธีการรักษาที่มิใช่มาตรฐาน ใช้การวิเคราะห์ถดถอยเอกนามและพหุนามเพื่อบ่งชี้ปัจจัยในการได้รับการรักษามาตรฐาน วิเคราะห์อัตราการอยู่รอดด้วยวิธี Kaplan-Meier และวิเคราะห์เพื่อเปรียบเทียบและบ่งชี้ปัจจัยในการอยู่รอดได้นานกว่าในระหว่างกลุ่มด้วยวิธี Cox-regression*

ผลการศึกษา*: มีผู้ป่วยที่เข้าเกณฑ์ในการศึกษาได้ทั้งหมด 318 ราย ผู้ป่วยส่วนใหญ่ได้รับการวินิจฉัยเป็นมะเร็งเยื่อบุผิวรังไข่ (ร้อยละ 89.9) ผลการตรวจทางพยาธิวิทยาส่วนใหญ่เป็นชนิด high grade serous (ร้อยละ 53.8) ผู้ป่วยส่วนใหญ่ได้รับการผ่าตัด (ร้อยละ 92.1) ชนิด primary cytoreductive surgery (ร้อยละ 72.4) และชนิด complete surgical staging (ร้อยละ 80.5) มีก้อนมะเร็งหลงเหลืออยู่ขนาดใหญ่กว่า 5 มม. ร้อยละ 42.3 อัตราการได้รับการรักษามาตรฐานและที่ไม่ใช่มาตรฐาน (ทั้งน้อยกว่าและมากกว่า) พบได้ร้อยละ 60.4 (ช่วงความเชื่อมั่นร้อยละ 95: ร้อยละ 54.9-65.6) และร้อยละ 39.6 ตามลำดับ ผู้ป่วยส่วนใหญ่ได้รับยาเคมีบำบัด (ร้อยละ 86.8) อัตราการอยู่รอดที่ 5 ปี และอัตราการอยู่รอดปลอดโรค เท่ากับร้อยละ 42.2 และ 26.8 อัตราการอยู่รอดโดยรวมในกลุ่มที่ได้รับการรักษาไม่ตรงตามมาตรฐาน ต่ำกว่ากลุ่มที่ได้รับการรักษามาตรฐานอย่างมีนัยสำคัญ (adjusted hazard ratio = 1.42, ช่วงความเชื่อมั่นร้อยละ 95: 1.01-2.02, p = 0.046)*

สรุป*: การรักษามะเร็งเยื่อบุผิวรังไข่ ควรปฏิบัติตามแนวทางการรักษามาตรฐาน เพราะอัตราการอยู่รอดโดยรวมในกลุ่มที่ได้รับการรักษาไม่ตรงตามมาตรฐาน ต่ำกว่ากลุ่มที่ได้รับการรักษาตรงตามมาตรฐานอย่างมีนัยสำคัญ*

คำสำคัญ*: การรักษามะเร็ง, ผลการรักษามะเร็ง, มะเร็งเยื่อบุผิวรังไข่, แนวทางเวชปฏิบัติ*

Introduction

Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in general population, accounting for more deaths than any other cancer of the female reproductive system[1]. Globally, the incident rate of new cases of ovarian cancer was 10.6 per 100,000 women per year. The estimated death in 2021 was 13,700, accounting for 2.3% of all cancer death. Approximately 1.1 percent of women will be diagnosed with ovarian cancer at some point during their lifetime[2]. In Thailand, breast cancer was the most common cancer in women (age-standardized incidence rate (ASR) = 34.2), and ovarian cancer was the third most common gynecologic cancers (under cervical cancer and endometrial cancer) with ASR = 6.0 leading to 53% deaths[3].

About half of the women who are diagnosed with ovarian cancer are elderly patients. Most of the cases are diagnosed in an advanced stage, which leads to poor outcomes of this disease. Ovarian cancer is often called the silent killer because the symptoms such as bloating, early satiety or bowel habits changes, are subtle. These could also be confused with other illnesses[4].

Two versions of national guidelines of epithelial ovarian cancer have been used in Thailand, which are NHSO (National Health Security Organization) 2018's[5] and TGCS (Thai Gynecological Cancer Society) 2019's[6] Adjuvant treatments have been mainly consisted of systemic chemotherapy (CMT), being considered from International Federation of Gynecology and Obstetrics (FIGO) stage and histologic grade. There was a study already done in Thailand[7] but only aspects of outcomes were evaluated in patients who underwent incomplete surgical staging, not any about the standard treatments' comparison.

Treatments of ovarian cancer might vary depending on the stage of the disease, histology, the performance status of the patient, expert opinion of the surgeon and patients' choice and their related outcomes are also depending on these factors. In the past, several studies in many countries had been done about the treatment that patients had been received compared with standard treatment according to the national guidelines[8-10]. The results were shown that many factors were associated with the lower rate of standard treatment, especially in elderly patients[8,9].

Treatments and their related outcomes had also never been evaluated in Srinagarind Hospital. Therefore, the objectives of this study were to compare treatments with national guidelines and oncological outcomes between standard and non-standard groups in real-life practice at Srinagarind Hospital.

Materials and Methods

This study was a retrospective descriptive analytical study conducted at Srinagarind Hospital, a tertiary hospital in Khon Kaen, Thailand. Study protocol was approved by Office of the Khon Kaen University Ethics Committee in Human Research on 14 June 2021 (HE641117). After then, this retrospective study was conducted.

The study was conducted in ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma patients diagnosed in Srinagarind Hospital from January 2014 to December 2019 by retrieving data from out-patient department (OPD) cards and health object (HO), the program to collect patients' data in electronics' pool. These data were then entered into a computerized database for subsequent analysis.

Inclusion criteria were all patients aged 18 years old or more who diagnosed as malignant neoplasms of ovary, fallopian tube, peritoneum during that period at Srinagarind hospital. Exclusion criteria were as follows; 1) surgeries were not done at Srinagarind Hospital, 2) final diagnoses were benign disease, 3) final diagnoses were borderline ovarian tumor, 4) final diagnoses were other primary origin or ovarian metastasis, 5) final diagnosis were germ cell, sex cord stromal, sarcoma, spindle cell and undifferentiated tumor, and 6) incomplete data recorded such as missed operative note.

The definition of "standard therapy" was that patients having surgery and/or chemotherapy as recommended in Thai national guidelines[5,6] based on the stage, histology and grade of the cancer. The definition of "non-standard therapy" was that patients not having "standard therapy". Only one deviation of the guideline would be interpreted as non-standard. However, pelvic without para-aortic lymphadenectomy could still be considered as standard therapy, as this was not mentioned in NHSO guideline[5]. Cessation of chemotherapy due to severe complication was considered as non-standard because the treatment was inadequate.

The rate of standard therapy rate was 80.0% from a previous study, with 95% confidence level and an error margin of 5%, the estimated sample size was at least 250. Table 1 shows the definition of standard treatment according to Thai national guideline recommended therapy.

Descriptive statistics were used to describe the demographic baseline characteristics. Numerical data were expressed as mean, standard deviation, percentages and 95% confidence interval (CI) to demonstrate the precision of the data. Categorical variables were expressed as percentages. Univariate and multivariate logistic regression was used to analyze odds ratio and adjusted odds ratio (adj OR), respectively. A p value of < 0.05 was considered statistically significant. Survival rate was analyzed by Kaplan-Meier method and overalls survivals were compared. Factors for longer survival were analyzed by Cox-proportional hazards model. All data analyses were performed using IBM SPSS statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Table 1. The definition of standard treatment according to Thai national guideline.

FIGO stage	Histology	Surgery (Primary cytoreductive surgery (PCS)/ Interval debulking surgery(IDS))	Chemotherapy	
			Number of Neoadjuvant cycles (PCS/IDS)	Number of Adjuvant cycles (PCS/IDS)
IA/IB	Low grade*, except clear cell carcinoma	PCS/IDS	None/2-4	None
	Clear cell carcinoma	PCS/IDS	None/2-4	3-8/3-6
	High grade**	PCS/IDS	None/2-4	3-8/3-6
IC	Any of above	PCS/IDS	None/2-4	3-8/3-6
II	Any of above	PCS/IDS	None/2-4	3-8/3-6
III	Any of above	PCS/IDS	None/2-4	3-8/3-6
IV	Any of above	PCS/IDS	None/2-4	3-8/3-6

* Endometrioid grade 1-2, low grade serous grade 1, mucinous carcinoma
** High grade serous grade 2-3, high grade endometrioid

Results

A total of 1,551 patients were recruited between January 1, 2014 and December 31, 2019. Not all were analyzed, due to 1,233 of them being excluded by the criteria mentioned above. Details of these exclusions were described in Fig. 1. Finally, there were 318 fully retrieved datasets for analyses. Mean follow-up time was 5 years (range 2-8 years, from January 2014 to December 2021). Overall survival rates at 1-, 3- and 5-year were 81.3%, 56.3%, and 42.2%, respectively. There were 166 recurrences (52.2%) in the whole cohort, therefore, the 5-year recurrence free survival rate was 26.8%. Median overall survival time was 3.6 years and

median recurrence free survival time was 0.83 years. Fig. 2 and 3 show overall survival times (OS) and recurrence free survival times (RFS) compared between standard and non-standard treatment.

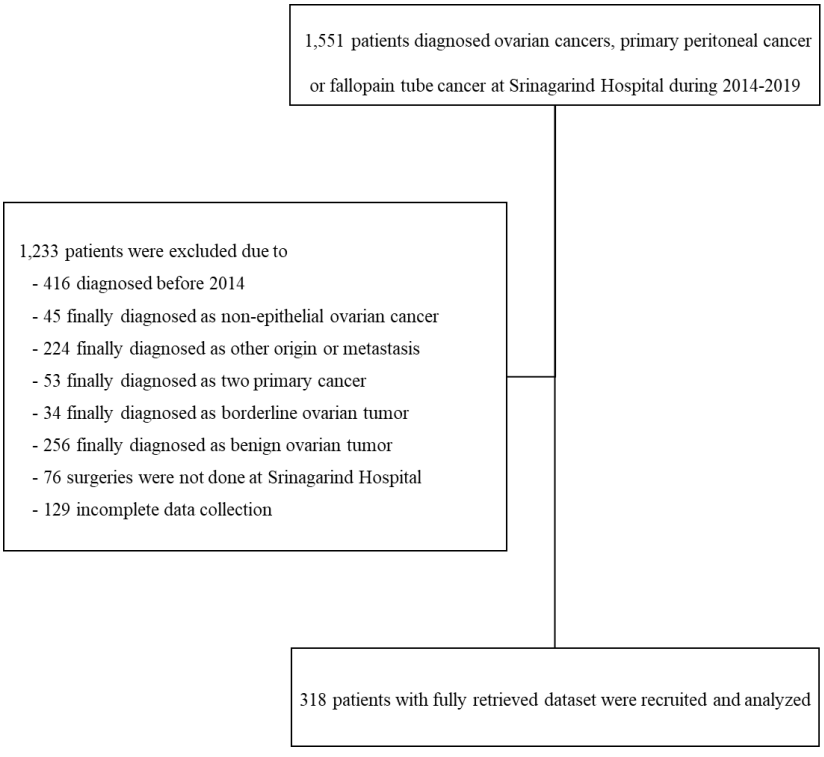

Fig. 1. Participants flow diagram.

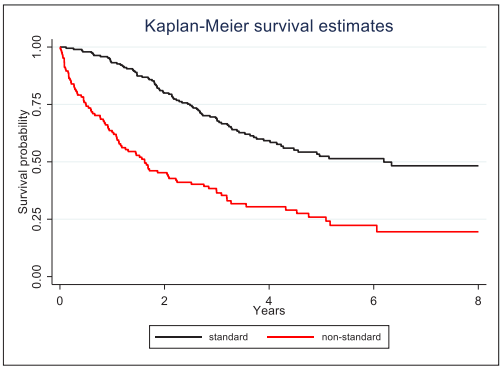

Fig. 2. Overall survival times (OS) compared between standard and non-standard treatment.

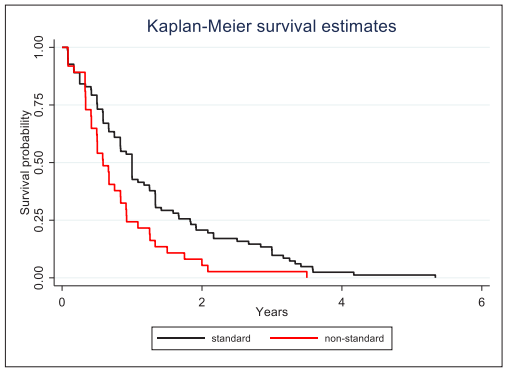

Fig. 3. Recurrence free survival times (RFS) compared between standard non-standard treatment.

Baseline characteristics were demonstrated in Table 2. Among 318 women diagnosed with ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma, 104 were elderly (> 60 years old). The mean age was 55.3 years. One third (28.6%) were nulliparity, and two third were post-

menopausal (73.9%). Most of them were married (78.0%) and had universal coverage (UC) and civil servant medical benefit scheme (CSMBC) as their health insurances (53.8% and 38.7%, consecutively). Mean body mass index (BMI) was 22.4 kg/m^2. Half of them had normal weight (53.8%), and at least 1 underlying disease (47.8%). Almost all (88.1%) of them were in class 0 of Eastern Cooperative Oncology Group (ECOG) performance status. Some of them had previous abdominal surgeries (14.8%).

Table 2. Baseline characteristics/ demographic data of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Baseline characteristics/ demographic data	n (%)
Age (years)	55.3
Parity	
- 0	91 (28.6%)
- 1	41 (12.9%)
- ≥ 2	186 (58.5%)
Menopausal status	
- Premenopausal status	83 (26.1%)
- Post-menopausal status	235 (73.9%)
Status	
- Single	65 (20.4%)
- Married	248 (78.0%)
- Divorced	5 (1.6%)
Health insurance	
- Universal coverage (UC)	171 (53.8%)
- Civil servant medical benefit scheme (CSMBC)	123 (38.7%)
- Social security scheme (SSS)	24 (7.5%)
- Self-pay	0 (0%)
Body mass index (BMI) categories	
- Underweight (BMI < 18.5)	45 (14.2%)
- Normal (BMI 18.5 - 22.9)	171 (53.8%)
- Overweight (BMI 23.0 - 24.9)	40 (12.6%)
- Obese (BMI > 25)	62 (19.5%)
Underlying disease	
- No	166 (52.2%)
- Yes	152 (47.8%)
Previous abdominal surgeries	
- No	271 (85.2%)
- Yes	47 (14.8%)
ECOG performance status	
- ECOG 0	280 (88.1%)
- ECOG 1	32 (10.1%)
- ECOG 2	3 (0.9%)
- ECOG 3	3 (0.9%)

ECOG: Eastern Cooperative Oncology Group

Pathological features were shown in Table 3. Most patients were diagnosed with epithelial ovarian cancer (89.9%), fallopian tube cancer and primary peritoneal adenocarcinoma were found in only 2.5% and 7.5%, consecutively. Over half of them were presented with advanced stage of disease (61.0%), 28.0% in stage IIIC and 21.1% in stage IVB. The majority of pathology was high grade serous adenocarcinoma (53.8%).

Table 3. Pathological features of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma cancers (n = 318).

Pathological features	Number	Application of guidelines-recommended therapy	
		Standard treatment	Non-standard treatment
Diagnosis			
- Ovarian cancer	286	176 (61.5%)	110 (38.5%)
- Fallopian tube cancer	8	7 (87.5%)	1 (12.5%)
- Primary peritoneal adenocarcinoma	24	9 (37.5%)	15 (62.5%)
Stages			
- IA	31	24 (77.4%)	7 (22.6%)
- IB	2	1 (50%)	1 (50%)
- IC	52	39 (75%)	13 (25%)
- IIA	6	6 (100%)	0 (0.0%)
- IIB	33	27 (81.8%)	6 (18.2%)
- IIIA	7	1 (14.3%)	6 (85.7%)
- IIIB	27	19 (70.4%)	8 (29.6%)
- IIIC	89	51 (57.3%)	38 (74.5%)
- IVA	4	2 (50%)	2 (50%)
- IVB	67	22 (32.8%)	45 (67.2%)
Histology			
- Low grade serous	8	7 (87.5%)	1 (12.5%)
- High grade serous	171	99 (57.9%)	72 (42.1%)
- Endometrioid	33	27 (81.8%)	6 (18.2%)
- Mucinous	23	15 (65.2%)	8 (34.8%)
- Clear cell	61	44 (72.1%)	17 (27.9%)
- Others/Unknown	22	0 (0.0%)	22 (100%)

Table 4 shows surgical treatment procedures. Surgeries were done in almost all of them (92.1%). Most surgical procedures were primary cytoreductive surgery (72.4%) and complete surgical staging (80.5%). Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) were done in most patients (90.4% and 93.5%, consecutively). Unilateral SO was performed in selected cases where the patients had fertility needed (4.8%). Omentectomies were done in 92.5%. Peritoneal cytology was done in 11.6%. Only some patients underwent bilateral pelvic node dissection or sampling (BPND/S) and para-aortic node dissection or sampling (PAND/S) (16.0% and 2.7%, consecutively). Residual tumors were left in 42.3% (suboptimal surgery). There was only 1 case that residual disease was not mentioned in the operative note. Other procedures such as appendectomy were performed in some cases (14.7%).

Table 4. Surgical treatments related procedures of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Surgical Treatments Related Procedures	n (%)
Surgery was not done	25 (7.9)
Surgery was done	293 (92.1%)
Surgery type	
- Primary cytoreductive surgery	212 (72.4%)
- Interval debulking surgery	81 (27.6%)
Surgery type	
- Fertility sparing surgery	16 (5.5%)
- Complete surgical staging	236 (80.5%)
- Incomplete surgical staging	41 (14.0%)
Residual disease	
- Optimal	169 (57.7%)
- Suboptimal	124 (42.3%)
Total hysterectomy (TH)	265 (90.4%)
Unilateral salpingo-oophorectomy (Unilateral SO)	14 (4.8%)
Bilateral salpingo-oophorectomy (BSO)	274 (93.5%)
Omentectomy	271 (92.5%)
Peritoneal cytology	34 (11.6%)
Bilateral pelvic node dissection or sampling (BPND/S)	47 (16.0%)
Para-aortic node dissection or dampling (PAND/S)	8 (2.7%)
Other procedures (adhesiolysis, appendectomy, peritoneal biopsy, random biopsy, etc.)	43 (14.7%)

Adjuvant treatments were classified in Table 5. Chemotherapies were given to most patients (86.8%), in which 34.4% were neo-adjuvant. Almost all (98.9%) were platinum-based with an average number of 4.1 courses. A total of 266 patients received adjuvant therapies (96.4%). Most of them (98.9%) received platinum-based chemotherapies with an average number of 5.5 courses.

Table 5. Chemotherapy treatments related procedures of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

No chemotherapy	**42 (13.2%)**
Chemotherapy	276 (86.8)
Neoadjuvant chemotherapy	
- Platinum based regimen (cases)	94
- Others regimen (cases)	1
- Mean of chemotherapy cycle (cycles)	4.1
Adjuvant chemotherapy	
- Platinum based regimen (cases)	263
- Others regimen (cases)	3
- Mean of chemotherapy cycle (cycles)	5.5

Treatments were classified in Table 6 depending on stages following FIGO staging in epithelial ovarian neoplasms. Application of guideline recommended therapy was found in 192 of 318 cases (60.4%), comparing with national treatment guidelines[5, 6]. In stage IA, there were 7 case (22.6%) that had non-standard treatment; including 5 cases that denied surgeries (3 cases due to advanced age and 2 cases due to fertility need), and 2 cases with incomplete staging. In stage IB, there was 1 patient (50%) receiving non-standard treatment due to adjuvant chemotherapy cessation after cycle 3 from severe neutropenia. In stage IC, there were 13 patients (25.0%) received non-standard treatment (10 cases due to incomplete surgical staging, and 3 cases due to adjuvant chemotherapy cessation from complications, which were severe neutropenia and hepatitis).

Table 6. Adjuvant treatments of ovarian cancers, fallopian tube cancers, and primary peritoneal adenocarcinoma (n = 318).

Stages	Number	Chemotherapy			Surgeries			Application of guidelines-recommended therapy		Recurrent
		No	NACT	Adj CMT	No	Primary cytoreductive surgery	IDS	Yes	No	
IA	31	13	0	18	0	31	0	24 (77.4%)	7 (22.6%)	4 (12.9%)
IB	2	0	0	2	0	1	1	1 (50%)	1 (50%)	0 (0%)
IC	52	2	4	50	0	48	4	39 (75%)	13 (25%)	9 (17.3%)
IIA	6	0	0	6	0	6	0	6 (100%)	0 (0%)	1 (16.7%)
IIB	33	0	7	33	0	27	6	27 (81.8%)	6 (18.2%)	10 (30.3%)
IIIA	7	3	1	4	2	4	1	1 (14.3%)	6 (85.7%)	5 (71.4%)
IIIB	27	0	16	27	0	13	14	19 (70.4%)	8 (29.6%)	19 (70.4%)
IIIC	89	1	46	86	0	47	42	51 (57.3%)	38 (74.5%)	67 (75.3%)
IVA	4	4	2	4	0	2	2	2 (50%)	2 (50%)	2 (50%)
IVB	67	19	18	35	23	33	11	22 (32.8%)	45 (67.2%)	49 (73.1%)
Total	318	42	276 (86.8%)		25	293 (92.1%)		192 (60.4%)	126 (39.6%)	166 (52.2%)

All patients in stage IIA had standard treatments according to standard guidelines. In stage IIB, there were 6 patients (18.2%) received non-standard treatments due to incomplete surgical staging. In stage IIIA, there were 6 patients (85.7%) received non-standard treatments due to denial for receiving surgery, denial for receiving chemotherapy, incomplete surgical staging, and others due to loss follow-up. In stage IIIB, there were 8 patients (29.6%) received non-standard treatments due to incomplete surgical staging. In stage IIIC, there were 38 patients (74.5%) received non-standard treatments due to incomplete surgical staging (19 cases), complication from chemotherapy (11 cases), and progressive disease during treatment (9 cases).

In stage IVA, there were 2 patients (50%) received non-standard treatment due to incomplete surgical staging. In stage IVB, there were 45 patients (67.2%) received non-standard treatments; 20 denied surgeries or chemotherapy due to advanced age and underlying disease, 3 had surgical complications (death), 14 had incomplete surgical staging, and 8 had progressive diseases during treatment.

Table 7 lists the factors associated with application of guidelines-recommended therapy. After the univariate and multivariate analyses were

performed by univariate and multivariate logistic regression, respectively. Age < 60-years-old (OR = 1.78, 95%CI: 1.11 to 2.87, p = 0.017, but adj OR = 1.69, 95%CI: 0.98 to 2.91, p = 0.06) and optimal surgery (adj OR = 4.64, 95%CI: 2.76 to 7.80, p < 0.001) were associated with received standard treatment.

Table 7. Factors associated with application of guidelines-recommended therapy.

Factors	Standard treatment applied = No		Standard treatment applied = Yes		OR (95%CI) p value	Adj OR* (95%CI) p value
	n	%	n	%		
Age						
≤ 60 years	75	59.52	139	72.4	1.78 (1.11 to 2.87) 0.017	1.69 (0.98 to 2.91) 0.06
> 60 years	51	40.48	53	27.6	1	-
Diagnosis						
Ovarian cancer	110	87.3	176	91.67	1	-
Fallopian tube cancer	1	0.79	7	3.65	4.38 (0.53 to 36.04) 0.17	-
Primary peritoneal adenocarcinoma	15	11.9	9	4.69	0.38 (0.16 to 0.89) 0.025	-
Stage	26	20.8	97	50.52	3.89 (2.32 to 6.52) < 0.001	
Early (I-II)	26	20.8	97	50.52	3.89 (2.32 to 6.52) < 0.001	-
Advance (III-IV)	99	79.2	95	49.48	1	-
Histology						
Low grade (G1-2)	13	10.32	45	23.44	2.66 (1.37 to 5.17) 0.004	-
High grade (G3, Clear cell)	113	89.68	147	76.56	1	-
Residual disease						
Optimal,	34	33.66	135	70.31	4.67 (2.79 to 7.82) < 0.001	4.64 (2.76 to 7.8) < 0.001
Suboptimal	67	66.34	57	29.69	1	-
Underlying disease						
No	66	52.38	100	52.08	1	-
Yes	60	47.62	92	47.92	1.01 (0.65 to 1.59) 0.959	-
Previous abdominal surgery						
No	105	83.33	166	86.46	1.28 (0.68 to 2.39) 0.443	-
Yes	21	16.67	26	13.54	1	-

* Multivariate logistic regression analysis
OR: odds ratio, CI: confidence interval

Survival of patients according to clinical and pathological features was shown in Table 8. Multivariate Cox-proportional hazards models were fit for each covariate with both survivals. There were 4 and 2 statistically significant prognostic factors for overalls survival time (OS) and recurrence free

survival time (RFS), consecutively, which consisted of advanced stages at diagnosis, received non-standard treatment (for both OS and RFS), suboptimal surgeries, and at least one underlying diseases (for OS only). The oncological outcomes (overall survival rate and recurrent free survival rate) were poorer in the non-standard group [adjusted hazard ratio (aHR) = 1.42 (95%CI: 1.01 to 2.02, p = 0.046) and aHR = 1.74 (95%CI: 1.14 to 2.61, p = 0.007), respectively].

Table 8. Survival of patients according to clinical and pathological factors.

Factors	Overall survival		Recurrence-free survival	
	HR (95%CI), p	aHR* (95%CI), p	HR (95%CI), p	aHR* (95%CI), p
Age				
≤ 60 years	1	-	1 (0.67 to 1.5), 0.988	-
> 60 years	1.45 (1.06 to 1.97), 0.018	-	1	-
Diagnosis				
Ovarian cancer	1		1	-
Fallopian tube cancer	0.76 (0.28 to 2.04), 0.581	-	2.09 (0.84 to 5.2), 0.113	-
Primary peritoneal adenocarcinoma	1.96 (1.2 to 3.19), 0.007	-	0.72 (0.36 to 1.44), 0.354	-
Stage				
Early (I-II)	1	1	1	1
Advance (III-IV)	5.7 (3.78 to 8.58), < 0.001	3.4 (2.17 to 5.32), < 0.001	1.66 (1.05 to 2.64), 0.031	1.66 (1.04 to 2.64), 0.033
Histology				
Low grade (G1-2)	1	-	1	-
High grade (G3, Clear cell)	2.51 (1.54 to 4.09), < 0.001	-	1.15 (0.66 to 2.01), 0.627	-
Residual disease				
Optimal,	1	1	1	-
Suboptimal	4.34 (3.08 to 6.1), < 0.001	2.38 (1.62 to 3.5), < 0.001	1.6 (1.1 to 2.31), 0.013	-
Underlying disease				
No	1	1	1	-
Yes	1.55 (1.15 to 2.1), 0.004	1.59 (1.15 to 2.2), 0.005	1.08 (0.75 to 1.56), 0.685	-
Previous abdominal surgery				
No	1.13 (0.73 to 1.76), 0.574	-	1.13 (0.67 to 1.92), 0.649	-
Yes	1	-	1	-
Therapy				
Standard	1	1	1	1
non-standard	2.72 (2.01 to 3.67), < 0.001	1.42 (1.01 to 2.02), 0.046	1.75 (1.17 to 2.6), 0.006	1.74 (1.17 to 2.61), 0.007

* Multivariate Cox-proportional hazards model. HR: hazard ratio, aHR: adjusted hazard ratio

Discussion

The aim of this retrospective study was to evaluate the treatment and outcomes in the patient diagnosed with epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma who received primary treatments at Srinagarind Hospital, one of the largest tertiary-care hospitals in Thailand. Authors clarified the types of treatment that epithelial ovarian cancer patients received in comparison between standard and non-standard according to national guidelines[5,6].

Authors included 318 patients diagnosed with epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma in Srinagarind hospital during 2014-2019. Patients' baseline characteristics/demographic data were quite similar among each group including age, parity, number of underlying diseases, health insurance, stages of the disease, histology and ECOG performance status.

The rate of receiving standard treatments was 60.4% (95%CI: 54.9-65.6%), which was lower than expected (80%). This rate differed from Bun et al's (78.7%),(8) but similar to Fourcardier et al's (63.3%). (9) This might be due to the two last versions of Thai national guideline on recommended therapy were published in 2018 and 2019, but authors studied on treatments since 2014.

Factors that associated with standard treatment were lower age (defined by a cut-off of 60-year-old in this study) and optimal surgery (Table 7). The elderly patients received standard therapies significantly less than the younger patients. These findings were similar to the previous studies. Bun et al[8] studied 244 patients with ovarian cancer stage I-IV in Japan and found that elderly patients (aged more than 70-year-old) received standard therapies less than younger patients (57.5% vs 81.2%). Fourcadier et al[9] studied 1,151 patients with all stage of ovarian cancer in France, also found that the elderly group (aged more than 70 years old) received standard therapies less than the younger group (52.0% vs 69.8%). This might be due to more underlying diseases, advanced stage at diagnosis, and less tolerance to chemotherapeutic toxicities in elderly patients.

In this study, authors also found that age (as defined by a cut-off of 60-year-old) was not a prognostic factor for either overall survival times and recurrence free survivals times, but the advanced stages of the disease at diagnosed and non-standard treatment were (Table 8). This was similar to another previous study. Yoshikawa et al[10] studied 114 patients with all FIGO stage ovarian cancers in Osaka city university hospital and found that prognostic factor for overall survival times were FIGO stage and standard primary therapy in younger group and were only performance status in elderly groups (defined by a cut-off of 70-year-old). Supporting by the rationale above, this was the possible reason why age was not found to be a significant prognostic factor in this study. Noticeably, the cut-off value for elderly patients in Thailand that author used was slightly lower than other studies because Thai life expectancy (LE) is lower.

For treatment outcomes, 5-years overall survival rate (42.2%) was slightly lower than the Thai previous study (57.0%)[7], but similar to worldwide reference (49.7%)[2]. In addition, this study's new findings to Thailand suggested that overall survival time and recurrent free survival time were poorer in the non-standard treatment with aHR = 1.42 (95%CI: 1.01 to 2.02, p = 0.046) and aHR = 1.74 (95%CI: 1.17 to 2.61, p = 0.007), respectively (Table 8).

The reason why non-standard treatment resulted in poorer survivals should be due to its less optimality. Optimal therapy means that patients had no residual disease after surgery and enough adjuvant platinum combination chemotherapy given in any appropriate cases. This is straightforward and was mentioned earlier in 2013 by Trilsch et al[11] as in their multivariate analysis, age itself was not a prognostic factor for PFS while the ECOG performance status had prognostic significance. In addition, these findings were supported later by many authors[8-10, 12-14].

Authors concluded that our rate of receiving standard treatment was comparable with France's (63.3%), but lower than Japan's (78.7%) and our expectation (80%). National guidelines on treatment

of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal adenocarcinoma should be followed, because of poorer outcomes in the non-standard groups.

The strengths of this study were as follows; first it was the second study about epithelial ovarian cancer treatment in Thailand with more detailed and larger sample size. Second, this study had adequate follow-up time with mean of 5 years (range 2-8 years) coverage of all epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma cases in Srinagarind Hospital, one of the largest tertiary-care hospitals in Thailand. Third, the sample size was adequate to detect oncological outcomes' differences between standard and non-standard groups.

Nevertheless, this study had some limitations. The analysis did not take factors such as details of underlying disease into account. Furthermore, no definite information about the reasons for non-standard treatment was available in retrieved study's data. Finally, this study was retrospective in nature, some biases might have occurred.

For practice and future research implications, collecting the reason for non-standard treatment and underlying diseases should be done. In addition, the correctable reason for non-standard treatment must be managed to optimize the effectiveness of treatments. Prospective data collection should be used.

Conclusion

Thai national guidelines on treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal adenocarcinoma should be followed, because of poorer outcomes in the non-standard groups.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Benign Multicystic Peritoneal Mesothelioma Discovered during Gynecologic Laparoscopic Surgery after Chemotherapy: A case report

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ABSTRACT

Benign multicystic peritoneal mesothelioma (BMPM) is an extremely rare intraperitoneal tumor that has been associated with endometriosis, pelvic inflammatory disease, and previous abdominal surgery. BMPM is a benign disease with an unknown etiology and clinical problems. The woman with no childbearing history developed intravascular large cell lymphoma at the age of 42 years, was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). After chemotherapy, the patient developed ovarian insufficiency, and gradually increased the left ovarian cyst of 7 cm in diameter. We planned laparoscopic bilateral adnexectomy to prevent left ovarian torsion and to search for pathology. After surgery, these cysts were pathologically diagnosed as BMPM. Problems of BMPM are high rate of recurrence, impairing quality of life and fertility due to causing in young age. Chemotherapy would be one of risk factor causing BMPM, since there are many reports of BMPM occurring in young women, gynecologists should take fertility into consideration when treating these patients.

Keywords: benign multicystic peritoneal mesothelioma, chemotherapy, infertility.

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Introduction

Benign multicystic peritoneal mesothelioma (BMPM) is an extremely rare intraperitoneal tumor that has been associated with endometriosis, pelvic inflammatory disease, and previous abdominal surgery[1]. BMPM is a benign disease with an unknown etiology and clinical problems such as a high recurrence rate, the possibility of malignant transformation, and lymph node metastasis[2]. It is difficult to diagnose and is often found incidentally during surgery[3], and there have been almost no reports in the field of gynecology. In this report, we describe a rare case of BMPM that was incidentally discovered during laparoscopic surgery after chemotherapy.

Case

A 46-year-old Japanese woman with no childbearing history developed intravascular large cell lymphoma at the age of 42 years, and was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and subsequently achieved remission. After chemotherapy, the patient developed ovarian insufficiency and was referred to the obstetrics and gynecology department where hormone replacement therapy was started. During the course of treatment and observation, a gradually increasing left ovarian cyst of 7 cm in diameter and an increasing serous cyst of 7 cm in diameter just below the fascia in the lower abdomen were noted (Fig. 1). Although the patient had no clinical symptoms, laparoscopic bilateral adnexectomy was planned to prevent left ovarian torsion and to search for pathology.

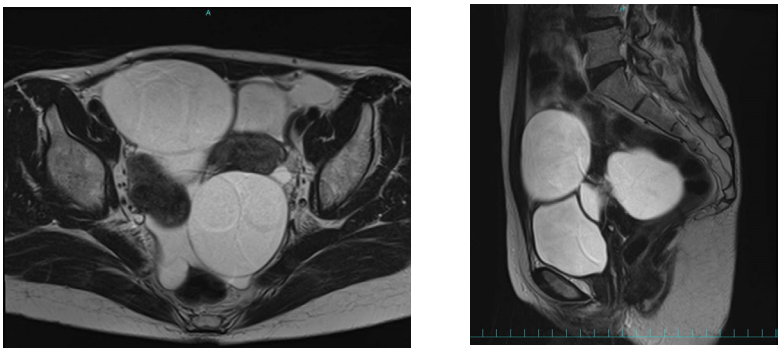

Fig. 1. MRI findings left ovarian cyst of 7 cm in diameter and a serous cyst of 7 cm in diameter just below the fascia in the lower abdomen.

Prior to laparoscopic surgery, a 7 cm serous cyst was found just below the fascia, which may have interfered with the laparoscopic approach, so the department of radiology was requested to aspirate the fluid from the cyst using interventional radiology. The contents were later found to have the same properties as a BMPM based on cytologic exploration. Laparoscopic surgery was performed in parallel approach, and intraperitoneal findings included a left ovarian cyst as well as colorless to pale yellow serous polycystic lesions scattered throughout the abdominal cavity. The cysts were extensively spread throughout the pelvic cavity, including the ovarian surface, fallopian tubes, peritoneum, omentum, and gastrointestinal tract (Fig. 2). The multiple cysts in the pelvis made it difficult to differentiate BMPM on preoperative imaging. After intraperitoneal observation, laparoscopic bilateral adnexectomy was performed as well as several biopsies of the polycystic lesions to complete the procedure. The pathological diagnosis of BMPM was made based on the positive

results of immunostaining for calretinin, podoplani, and Wilms' tumour protein (WT-1) and negative results for cluster of differentiation 31 (CD31) (Fig. 3). The patient was discharged on the fourth postoperative day in good general condition. The BMPM was referred to a gastrointestinal surgeon at another hospital, and the subfascial cyst was aspirated according to abdominal symptoms.

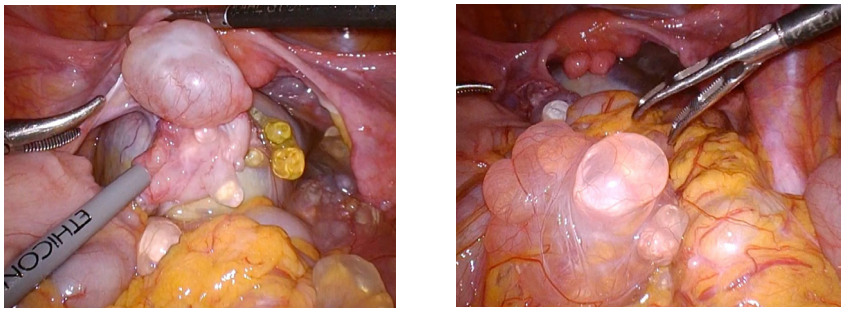

Fig. 2. Laparoscopic finding: the cysts were extensively spread throughout the pelvic cavity, including the ovarian surface, fallopian tubes, peritoneum, omentum, and gastrointestinal tract.

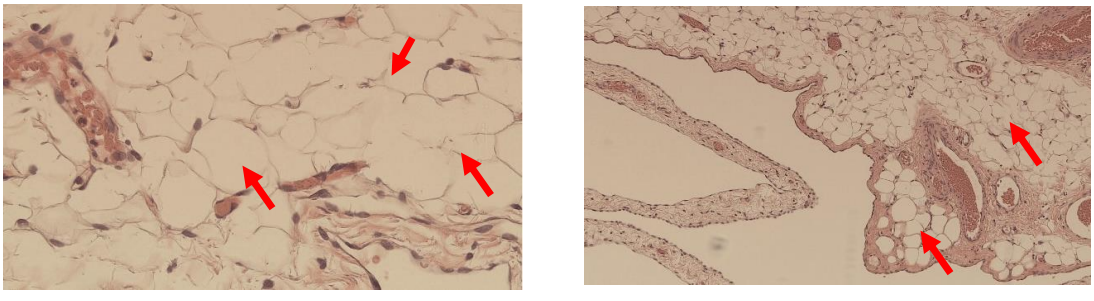

Fig. 3. The pathological diagnosis of benign multicystic peritoneal mesothelioma based on the positive results of immunostaining for calretinin, podoplani, and WT-1 and negative results for CD31.

Discussion

BMPM was first described by Menemeyer and Smith in 1979[4]. It is often difficult to diagnose preoperatively because it may be discovered incidentally during surgery. MRI is the best imaging technique for BMPM but definitive diagnosis relies primarily on histopathological examination and immunohistochemistry, especially, the D2-40 stain can strongly promote a diagnosis of BMPM[1].

While surgical removal of the tumor en bloc is recommended as the primary treatment strategy[1], Alpár György reported a high recurrence rate of 50% for BMPM[5]. Thus, recently BMPM is considered as a borderline malignant neoplasm because of high recurrence rate[1]. Eran Nizri reported that, in addition to surgery, hyperthermic intraperitoneal chemotherapy (HIPEC) is effective[6]. Pathologic diagnosis is difficult[7], and differentials include lymphangioma, peritoneal pseudomyxoma, endometriosis, ovarian cystadenoma or cystadenocarcinoma, cystic teratoma, and other large mesenteric cysts, and differentiation from malignant mesothelioma is most important issue[1].

Risk factors for developing BMPM include being female, having endometriosis, leiomyoma, pelvic inflammatory disease, and a history of abdominal

surgery of either sex[3]. Genetic association has been suggested, but no clear responsible gene has been identified. Of note, malignant transformation is a possibility, but is reported to be infrequent and is often observed in the absence of symptoms. The present patient had no pelvic inflammatory disease, history of surgery or medical history of endometriosis, but had received chemotherapy several years before onset of disease. In other reports, BMPM has been reported incidentally after referral to obstetrics and gynecology after early menopause due to postoperative adjuvant chemotherapy for breast cancer, suggesting that chemotherapy may be involved in the development of BMPM[2]. Several physicians believe that reactive etiology is the etiology, and the presence or absence of chemotherapy, especially in young women, may be a risk factor for BMPM[8].

There are few reports in the field of gynecology that point to an association between BMPM and ovarian tumors. Thus, gynecologists should be aware of the presence of BMPM when they discover multiple cystic lesions in the abdominal cavity preoperatively or intraoperatively, taking risk factors into consideration. If clinical symptoms develop, surgical treatment should be considered according to the patient's quality of life. In principle, complete surgical resection is recommended, but such as the present case, where there are no symptoms and complete removal is difficult because the tumor has spread throughout the abdominal cavity, partial removal may be acceptable according to pathological exploration purposes and reducing symptoms. In addition, malignant transformation rate is extremely low. The patient's treatment history, including chemotherapy, should be taken into consideration. Since there are many reports of BMPM occurring in young women, gynecologists should take fertility into consideration when treating these patients. The frequency of BMPM has not been systematically reported, and the accumulation of future cases may help guide treatment.

Potential conflicts of interest

The authors declare no conflicts of interest.

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