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EDITORIAL

Intriguing Review and Topics in Second Issue of Thai Journal of Obstetrics and Gynaecology 2026

Vorapong Phupong, M.D., FRTCOG.*

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

This second issue of Thai Journal of Obstetrics and Gynaecology 2026 contains many interesting articles. The special article is "Reproductive health in adolescent women". The topics included physiological changes in adolescent girls and women, adolescent contraception, sexually transmitted infections in adolescent girls and women, and adolescent pregnancy[1].

This issue also contains seven original articles. Tomuen et al performed a single-blind randomized controlled trial to evaluate the efficacy of postoperative chewing gum in promoting gastrointestinal recovery following complete surgical staging for gynecologic malignancies. The results showed chewing gum significantly reduced the time to first flatus in women undergoing complete surgical staging for gynecologic malignancies[2].

Paibulsirichit et al performed a prospective cohort study to evaluate the impact of intramuscular pethidine on labor duration as well as associated maternal and neonatal outcomes. They found intramuscular pethidine administration significantly shortened the active phase of the first stage of labor compared to the non-pethidine group after adjusting for confounding factors, without increasing adverse maternal or neonatal outcomes[3].

Wattanacharoen et al performed a single-center, open-label, randomized controlled trial to compare outcomes of a cyst or abscess of the Bartholin gland after surgical treatment using a modified Word catheter or marsupialization. They found women with a Bartholin gland cyst or abscess, treatment with a modified Word catheter provides similar recurrence rates to marsupialization, but with shorter procedural time and less perioperative pain[4].

Munjal et al performed a three-year study to compare the percentage and absolute numbers of peripheral blood (PB) natural killer (NK) cells and its subsets and levels of T helper cells 1 cytokines [interferon-gamma and tumor necrosis factor-alpha] in women with unexplained infertility with that of healthy fertile women. The results showed CD56+CD16+ NK cells which constitute the major population of PB NK cells and its major subset, CD56dim CD16+ NK cells was significantly raised in unexplained infertile women[5].

Khorprasert et al performed a prospective cross-sectional study to compare the prevalence of illicit drug use during pregnancy between teenage and non-teenage, to investigate the possible factors predicting of illicit drug use before and during pregnancy and also to compare the incidence of adverse maternal/neonatal outcomes and overall adverse pregnancy outcomes between the participants who had a history of illicit drug use during pregnancy and those who did not. They found prevalence of illicit drug use during pregnancy in

teenagers was not different from in non-teenagers. The level of education of junior high school or lower, more than 7 hours per day social media use, and a young age at first sexual intercourse were significant factors associated with a higher prevalence of illicit drug use during pregnancy[6].

Pariyanont et al performed a cross-sectional study to evaluate the correlation between the total dosage and duration of maternal magnesium sulfate ($MgSO_4$) administration and umbilical cord blood magnesium levels, and to determine clinically useful cutoff values associated with elevated neonatal magnesium concentrations. The result showed both the total dosage of $MgSO_4$ and infusion duration were strong predictors of neonatal cord blood magnesium levels. Two clinically useful cutoff values for predicting cord magnesium ≥ 5 mg/dL were a total dose of 12.8 and an infusion duration of 280 minutes[7].

Xanthavanij et al performed a retrospective study to determine the prevalence and the associated risk factors of endometrial hyperplasia and endometrial cancer in women with abnormal uterine bleeding and body mass index less than 30 kg/m^2. They found the prevalence of endometrial hyperplasia and endometrial cancer was total 9.2%. Postmenopause and woman older than 60 years old were independently associated with endometrial hyperplasia and endometrial cancer[8].

The RTCOG midyear meeting will be held during 21 - 24 April 2026 at Centara Grand at Central Plaza Ladprao, Bangkok, Thailand. The theme of the meeting is "Redefining the Future of Women's Health". Wish to see you at RTCOG midyear meeting 2026 at Centara Grand at Central Plaza Ladprao, Bangkok, Thailand.

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SPECIAL ARTICLE

Reproductive Health in Adolescent Women

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ABSTRACT

Adolescence is a crucial period in human life. Several changes have occurred. Understanding the physiological and emotional changes that occur in adolescent girls and women (GW) and also knowing and having comprehensive knowledge on the common issues that adolescent GW often seek care for in order to provide them correct and appropriate care. According to several studies, health problems will follow sexual intercourse. Thus, adolescent GW should be encouraged to have no sex as the first choice. If adolescents have sex, encourage them to use effective contraception, along with condoms, to protect them from the sexually transmitted infections.

Keywords: Adolescence, girl, reproductive, sex, development.

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Introduction

Adolescence refers to a girl/woman (GW) between the ages of 10 and 19 years[1]. Generally, adolescent GW are growing up under the care of their parents, families, and educational providers. These adolescent GW are the nation's hope to become the most valuable key persons for the future development of the nation. Adolescence is a period of change in several aspects, especially physical, emotional, and behavioral that may influence their relationships with people and the environment around them. Therefore, proper care from parents/families and surrounding adults, along with welfare support from the government, is likely to help them grow and live a quality life. Initially, health care providers should understand the physiological and emotional changes that occur in adolescent GW and also know and have comprehensive knowledge of the common issues that adolescent GW often seek care for in order to provide them with correct and appropriate care. This article is categorized into sections covering the physiologic change in adolescent GW, adolescent GW in Thailand, and common issues

frequently addressed by adolescent GW, including adolescent contraception, pregnancy-related health care, care-seeking for care, and testing for sexually transmitted infections (STIs)[1].

Physiological changes in adolescent GW

The adolescent GW period typically spans from 10/11 years old (ranging from 8 to 13 years) and encompasses a duration of 6 years until stopping at around 17/18 years old[2]. During the first 3-year period (junior high school), physical development rapidly presents and then gradually matures until it nearly reaches an adult level around high school[2]. Physiologic changes in adolescent GW are described as follows[3]:

1. Physical characteristics: Height, weight, and body image show changes. Rapid height increasing, or growth spurts, begin on average at 10-11 years old (range 8-13 years old), and they reach their adult level around 10-16 years old[3]. Individual adult height depends on several factors, including genetics, nutrition, medical condition, and medication[3]. Asian ethnicity tend to have limbs (arms and legs) that are slightly shorter relative to their trunk (torso)[4]. Widening of the hip is also observed. Consuming adequate and balanced nutrition is one of the most important factors influencing the onset and progression of pubertal development. Excessive intake of some types of protein, fat, minerals, and vitamins may lead to early puberty. Malnutrition of essential amnio acids, calorie deprivation and some micronutrient deficits can delay the progress of growth and bone maturation, cause physical growth retardation, reduce intellectual capacity, and increase the risk to infections. There is some literature review suggesting that increased caloric, protein, iron, calcium, zinc, and folate needs must be arranged during the critical period of rapid linear growth and bone maturation[5].

2. Breast development: Usually, breast development is the first visible secondary female sexual characteristic. It occurs around 10 years old and takes several years to gradually develop to an adult state. Parents should provide the proper bra, a soft crop top, or a sports bra to adolescent GW[3].

3. Axillary hair and facial acne: Axillary hair usually grows following the breast development initiation[3]. Facial acne occurs because of the overactivity of sebaceous gland function. Moreover, increasing sweat glands can lead to body odor. These cosmetic appearances and body odors may affect adolescent self-esteem[6]. Counselling for hygiene care is important.

4. External genitalia (vulva and pubic hair): Enlargement of external genitalia and growth with darkening and thickening of pubic hair are observed in adolescent GW.

5. Internal reproductive organs and menstruation: Pubertal development can be divided into gonadarche and adrenarche development, depending on the different hormone influences[7]. Gonadarche is the process of reactivation of the hypothalamic-pituitary-ovarian axis. Synthesis of gonadotropin-releasing hormone, luteinizing hormone and follicle-stimulating hormone initiated the pubertal process. The ovary starts estrogen production. Estrogen is the main hormone for female adolescent development. Estrogen controls the breast stage development, vaginal keratinization, and uterine growth. Clear white secretion presents from the adolescent GW vagina several months before their menarche (the 1st menstrual period). Proper use of panty liners or underwear should be provided and advised. Adrenarche is the development of pubic/axillary hair and sebaceous gland function[2].

6. Brain and cognitive: The brain has developed both in size and maturation. 7 things to know about the teen brain are as follows:[8]

- Adolescence is an important time for brain development. Growing in size during the early adolescent period and then followed by fine-tuning how the brain works.

- Brain development is related to social experiences during adolescence. Emphasis on peer relationships could be developed in both negative (dangerous) and positive ways. Positive relationships, such as joining a sport and proper classmates, should

be provided.

- The teen brain is ready to learn and adapt. Encourage taking challenging classes, exercising, and creative activities.

- Teen brains may respond differently to stress.

- Most teens do not get enough sleep. Adolescent melatonin (sleep hormone) levels are secreted in a different way from those of children and adults. It may explain why many adolescent GW stay up late and struggle with getting up in the morning. About 9-10 hours of sleep a night should be advised. A lack of sleep can make them have difficulty to paying attention and increase impulsiveness and irritability or depression[3].

- Several mental illnesses may begin in adolescent GW.

- The teen brain is resilient.

Adolescent GW in Thailand

The Bureau of Registration Administration (BORA), Thailand, reported the number of Thai adolescent GW in January 2025. The number of early adolescent GW (11-15 years old) and late adolescent GW (16-20 years old) were 1,878,377 and 1,940,449 persons, respectively. The number of adolescent GW trends decreased compared to the past because the birth rate continuously reduced[9].

Adolescent contraception

Sexual intercourse in adolescent GW has been concerned in several aspects, such as unintended pregnancy, sexually transmitted infections (STIs), and violence[10]. Thus, proper contraception counselling, prescribing, and management are important skills that gynecologists, general practitioners, pediatricians, and health care providers should able to perform effectively. The report about adolescent pregnancy in Thailand in the years 2024-2026 from the Bureau of Reproductive Health, Ministry of Public Health, presented that the most common maternal age of adolescent pregnancy was 15-19 years old. Most of them got pregnant while learning in high school[11]. Factors that were found to be the risk of early sexual activity in adolescents were low socioeconomic status, living in a single-parent home, engaging in risk-taking behavior (illicit drug use), etc[12]. Moreover, the association of long-duration use of social media (more than 7 hours a day) was associated with illicit drug use[13]. A specific law in Thailand regarding prescribing contraception to adolescent GW was announced in the year 2019 that adolescent GW over the age of 15 can access contraceptive services by themselves without the consent or permission of their parents.

Anyway, we remain to encourage the adolescent GW to have this discussion with their parents about contraceptive risks, and it also assists in satisfying the competence decision. The important issues about adolescent contraception are categorized according to contraceptive types as follows:

- Combined oral contraceptive pill (COCP): It is short-term contraception, has a chance of unintended pregnancy, and cannot protect and prevent STIs. A previous study found that 39% of unintended pregnancies occurred while using COCP[14]. It has the benefit of regulating menstruation and timing, reducing dysmenorrhea and acne, and controlling hirsutism. The cost and availability are advantages. There is no evidence that COCP impacted the development of the female reproductive system[15]. Caution should be concerned in an adolescent GW at risk for mood disorder because it appears to be increased in rates of depression[15].

- Depot medroxyprogesterone (DMPA): It is a long-acting hormonal method. Thus, no need for daily compliance and no interruption of the sexual arousal process are the advantages. Anyway, it still requires visiting the health care provider, and menstrual cycle irregularities are concerned. Menstrual irregularity/spotting occurs in around 25-50% of 12-week DMPA users in the first 6-12 months after initiation[16]. Then, most DMPA users become amenorrheic or oligomenorrheic. Some adolescent GW felt it to be a positive aspect of DMPA[12]. Historically, the concern was about bone mineral density (BMD); it is now generally accepted that decreasing in expected BMD

is reversible after DMPA discontinuation[17].

- Barrier methods (condom): Condoms are not a recommended contraceptive method for adolescent GW because failure rates with barrier methods reach 18-21 pregnancies per 100 in a year with typical use[15]. However, condoms are still an important way for STIs prevention[15].

- Subdermal implant (Implanon®): Efficacy for pregnancy prevention is excellent. The failure rate of these long-acting reversible contraceptives was reported to be only 0.001%, which is superior even to tubal ligation[18]. It is of limited use in case of disclosure using requests because it is physically obvious.

- Emergency postcoital contraception: It should not be recommended for routine use. It is limited to adolescent GW who has had unprotected sexual intercourse in the prior 72 hours, such as victims of sexual assault and individuals whose usual method failed (broken condom). Moreover, baseline pregnancy tests and STIs screening and prophylaxis should be provided.

- Intrauterine device (IUD): An IUD is a highly effective contraception method, with a success rate of 98-99%[19]. Although concerns about IUD insertion in women at risk of STIs have decreased because the previous studies have shown it does not increase the incidence of pelvic inflammatory disease[20]. High risk for STIs: Adolescents should be careful to be IUD users. Lastly, IUD use has not been found to compromise infertility[21].

Sexually transmitted infections (STIs) in adolescent GW

According to the Centers for Disease Control and Prevention recommendation, prevention of STIs in adolescent GW should be applied to all adolescent GW as follows:

- The healthcare provider should give the adolescent GW time alone for assessment of their sexual behavior and identify their high individual risk for STIs such as substance misuse, exchanging sex for drugs or money, and multiple sex partners.

- In United States of America, routine screening for Chlamydia trachomatis and Neisseria gonorrhoeae is recommended for all sexually active females aged less than 25 years[22]. In Thailand, there is no routine gonococcal and chlamydial infection.

- Human Papilloma Virus (HPV) vaccination is recommended. In Thailand, Thai adolescent girls aged 11-12 years have been receiving the HPV vaccine as a part of the national public health policy since 2017.

- Hepatitis A and B vaccination (HAV, HBV) series should be recommended to adolescent GW who have not previously received the universal HAV or HBV series during their childhood[23].

- All adolescent GW should receive comprehensive knowledge and information about human immunodeficiency virus (HIV) infection regarding the following topics: how it is transmitted, prevention, HIV PrEP (pre-exposure prophylaxis) and diagnostic testing.

Moreover, we suggest that sexual knowledge should be integrated into the educational curriculum for adolescent GW since their junior high school level.

Adolescent pregnancy

Globally, around 11% of births are to girls aged 15 to 19, and 95% of these are in low- and middle-income countries[24]. Since 1989, Thailand's adolescent birth rate has declined from 70 to 43 births per 1000 in 2008 and lastly 31.7 in 2021[25, 26]. Pregnancy concern risk is described:

- Unintended pregnancy and sometimes induced abortion requests. According to Thai law, induced abortion can be provided for unintended pregnancy at a gestational age of less than 12 weeks. The aim of the law is to prevent the adolescent GW from the dangerous process of illegally induced abortion[27].

- Adolescent pregnancy increased several adverse pregnancy and neonatal outcomes such as preterm birth, cesarean section, neonatal low birth weight, and neonatal death[28-30]. Thus antenatal and intrapartum care for high-risk pregnancy must be

performed.

- A previous study found that infants of adolescent mothers who have inadequate prenatal care are at increased risk of neonatal intensive care unit admission, have low Apgar scores and require long hospital stays[31].

Conclusion

In conclusion, health care providers should encourage adolescent GW not to have sex; it should be the first choice. If adolescents have sex, encourage them to use effective contraception, along with condoms to protect them from STIs.

Potential conflicts of interest

The authors declare no competing interests.

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GYNAECOLOGY

Effect of Gum Chewing on Gastrointestinal Function after Complete Surgical Staging in Gynecologic Malignancies: A Randomized Controlled Trial

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ABSTRACT

Objectives: To evaluate the efficacy of postoperative chewing gum in promoting gastrointestinal recovery following complete surgical staging for gynecologic malignancies.

Materials and Methods: A single-blind randomized controlled trial was conducted in women who underwent complete surgical staging for gynecologic malignancies. Participants were randomly assigned to two groups. The intervention group received the sugar-free chewing gum for 15 minutes, four times per day, in addition to standard postoperative care, while the control group received standard postoperative care. The primary outcome was the time to first flatus.

Results: From July 2024 to March 2025, 68 participants were enrolled in this study. The chewing gum group showed significantly shorter time to first flatus compared to the control group (33.5 ± 11.7 hr vs 42.7 ± 11.7 hr, mean difference -9.2 hr, 95%CI -14.9, -3.6, p = 0.002). Furthermore, the use of additional anti-emetic drugs was significantly lower in the chewing gum group [3 (8.8%) vs 11 (32.4%), p = 0.036]. No significant differences were observed in time to first defecation, postoperative nausea, postoperative vomiting, and additional analgesic use. No serious adverse effects were reported in this study.

Conclusion: Chewing gum significantly reduced the time to first flatus in women undergoing complete surgical staging for gynecologic malignancies.

Keywords: chewing gum, postoperative bowel function, gynecologic malignancy, surgical staging.

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ประสิทธิภาพของการเคี้ยวหมากฝรั่งเพื่อกระตุ้นการทำงานของลำไส้หลังการผ่าตัดโรคมะเร็งทางนรีเวช

ภัทรปภา โตเหมือน, กิติยา วุฒิเบญจรัศมี

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการเคี้ยวหมากฝรั่งเพื่อกระตุ้นการทำงานของลำไส้หลังการผ่าตัดทางมะเร็งนรีเวช*

วัสดุและวิธีการ: *การศึกษานี้เป็นการทดลองแบบสุ่ม โดยมีประชากรตัวอย่างเป็นผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งทางนรีเวชวิทยาและเข้ารับการผ่าตัดเพื่อกำหนดระยะโรค โดยผู้เข้าร่วมวิจัยถูกแบ่งเป็น 2 กลุ่ม โดยใช้การสุ่ม โดยกลุ่มทดลองจะได้รับหมากฝรั่งแบบปราศจากน้ำตาล เคี้ยวเป็นเวลา 15 นาที 4 ครั้งต่อวัน หลังการผ่าตัด ส่วนกลุ่มควบคุมจะได้รับการดูแลตามมาตรฐานวิชาชีพหลังการผ่าตัด ผลลัพธ์หลัก คือ ระยะเวลาจนถึงการผายลมครั้งแรก ผลลัพธ์รอง ได้แก่ ระยะเวลาจนถึงการถ่ายอุจจาระครั้งแรก อาการคลื่นไส้อาเจียน การใช้ยาบรรเทาอาการปวด และการใช้ยาบรรเทาอาการคลื่นไส้อาเจียน*

ผลการศึกษา: *จากเดือนกรกฎาคม 2567 ถึงมีนาคม 2568 จำนวนผู้เข้าร่วมวิจัยมีทั้งหมด 68 คน โดยพบว่า ประชากรกลุ่มทดลองที่เคี้ยวหมากฝรั่ง มีระยะเวลาจนถึงการผายลมครั้งแรกสั้นกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (33.5 ± 11.7 กับ 42.7 ± 11.7 ชม., ความแตกต่างเฉลี่ย -9.2 ชม., 95%CI -14.9 ถึง -3.6, p = 0.002) และการใช้ยาบรรเทาอาการคลื่นไส้อาเจียนพบว่าน้อยกว่าในกลุ่มที่เคี้ยวหมากฝรั่งเทียบกับกลุ่มควบคุม [3(8.8%) กับ 11(32.4%), p = 0.036] ผลลัพธ์รองอื่นๆ ได้แก่ ระยะเวลาจนถึงการถ่ายอุจจาระครั้งแรก อาการคลื่นไส้อาเจียน การใช้ยาบรรเทาอาการปวด ไม่พบความแตกต่างอย่างมีนัยสำคัญ และไม่พบผลข้างเคียงร้ายแรงจากการเคี้ยวหมากฝรั่งในการศึกษานี้*

สรุป: *การเคี้ยวหมากฝรั่งหลังจากการผ่าตัดเพื่อกำหนดระยะโรคในผู้ป่วยมะเร็งนรีเวชสามารถลดระยะเวลาจนถึงการผายลมครั้งแรกได้อย่างมีนัยสำคัญ*

คำสำคัญ: *การเคี้ยวหมากฝรั่ง, ภาวะลำไส้อุดตันหลังการผ่าตัด, มะเร็งนรีเวช, การผ่าตัดเพื่อกำหนดระยะโรค*

Introduction

Postoperative bowel ileus is defined as the intolerance of oral intake due to non-mechanical factors that inhibit bowel activity, which leads to fluid and gas accumulation in the gastrointestinal tract, resulting in clinical features including abdominal distension, nausea, vomiting, and absence of bowel sounds[1]. Pathophysiology of postoperative bowel ileus remains unclear, but it is believed that many mechanisms may contribute to this condition, such as involvement in the neurogenic process by inhibiting neural reflexes, leading to the inhibition of sympathetic activity, inflammatory mediators, and pharmacological mechanisms such as using opioids during anesthesia, which may stimulate the inflammatory process causing the delay of gastrointestinal function[2]. It is usually self-limiting within 24-72 hours after abdominal procedures. Still, prolonged postoperative bowel ileus can be affected by the delay of early feeding, immobilization, prolonged hospitalization, and increased cost of stays[3].

Gynecological cancers are a significant health concern and remain a substantial health burden, giving rise to over a million new cases and hundreds of thousands of deaths per year for women worldwide[4]. Surgery remains the principle of gynecological cancer treatment, especially in the early stage. Due to the prolonged duration of the operation, a large abdominal incision, and difficulty of operation procedures, postoperative bowel ileus is found in 10.6% to 50% of patients with gynecologic staging surgery[5].

In Thailand, several modalities aimed at enhancing postoperative bowel recovery have also been investigated in gynecologic surgery, with findings that vary across interventions[6-10]. Some approaches, such as metoclopramide and oral ginger powder, have shown evidence of promoting earlier return of bowel function, whereas others, including caffeine, preoperative walking exercise, and ginger supplementation within an enhanced recovery after surgery (ERAS) protocol, did not demonstrate significant improvement. These mixed results reflect ongoing efforts to identify simple and low-cost strategies to support postoperative gastrointestinal motility, though the overall effectiveness of these interventions remains inconsistent.

Gum chewing is hypothesized to prevent postoperative bowel ileus by mimicking food intake and then affecting the gastrointestinal tract as normal feeding through the cephalic-vagal pathway[11]. Additionally, chewing gum increases the concentration of gastrin, neurotensin, and pancreatic polypeptide, which promotes gastrointestinal motility[12]. Hence, it is a simple and cost-effective alternative treatment for promoting recovery of bowel function after gastrointestinal surgery[13-14] and cesarean section[15-18]. Evidence regarding gum chewing after surgery for gynecologic malignancies remains limited. While most studies[19-21] in gynecologic oncology have employed a 30-minute chewing protocol, some investigations in benign gynecologic surgeries[22] have demonstrated that a 15-minute chewing session can significantly reduce the time to first flatus, an established marker of bowel recovery. To minimize chewing time and enhance patient compliance, this study aimed to evaluate whether a 15-minute gum chewing regimen following complete surgical staging for gynecologic malignancies can effectively promote the return of gastrointestinal function.

Materials and Methods

The study aimed to examine the efficacy of 15-minute gum chewing postoperatively in encouraging the return of gastrointestinal function for preventing postoperative bowel ileus. The study was designed as a single-blind randomized controlled trial, conducted at Khon Kaen Hospital. The data were collected from July 2024 to March 2025.

The study included patients who were 18 years or older, undergoing complete surgical staging in gynecologic malignancies, which were endometrial cancer, ovarian cancer, and other, e.g., peritoneal cancer (total abdominal hysterectomy with bilateral salpingo-oophorectomy with bilateral pelvic lymph node dissection with omentectomy with peritoneal washing ± paraaortic dissection ± peritoneal biopsy),

good consciousness, and communicated in Thai fluently. Women who were unable to chew, on removal dental prosthesis, severe dental caries or loose teeth, mint allergy, poor cognitive function, risk of choking or dysphagia, major bowel surgery e.g. history of end-to-end anastomois bowel, colostomy, chronic diseases requiring anti-cholinergic drugs for treatment e.g. chronic obstructive pulmonary disease, Parkinson's disease, irritable bowel syndrome and psychiatric disorder were excluded from this study.

The patients received the same preoperative evaluation and management, including a clear liquid diet and bowel preparation with polyethylene glycol balanced electrolyte solution (Niflec®) 1 pack (137.55 g) in water 2 L, then drank within two hours before midnight. Prophylaxis embolization was allowed according to the Caprini score (low molecular weight heparin/ intermittent pneumatic compression). Patients were not allowed to receive any food after midnight before surgery.

All patients underwent the same anesthetic technique by standard general anaesthesia with a transabdominal plane block containing 1% lidocaine with adrenaline and 0.025% bupivacaine, which corresponds to the maximum dose of 7 mg/kg lidocaine with adrenaline and 3 mg/kg bupivacaine being injected between the transversus abdominis and internal oblique with ultrasound guidance. The participants received prophylactic intravenous antibiotics at the time of induction of anaesthesia, which consisted of either cefazolin 2 gm or clindamycin 900 mg in cases of penicillin allergy. The surgery was performed by oncologic gynecologists at Khon Kaen Hospital using the same standard surgical staging procedure. Types of incisions were low midline, Pfannensteil, and Maylard incisions, based on the patient's condition.

Following the operation, the allocation of treatment was determined in a consecutive order by the doctors. The participants were randomized using a computer-generated block of four, prepared in numbered, sealed envelopes. The study was only blinded to the outcome assessor until the data were analyzed. The patients in the intervention group (Group A) received sugar-free chewing gum (Xylitol®) the day after surgery every 4 hours. Continuously chewing one piece of gum lasts for 15 minutes, 4 times per day, starting at 6:00 am, 10:00 am, 2:00 pm, and 6:00 pm. (except bedtime). The postoperative chewing process continued until either the first flatus occurred or 72 hours after the operation. The control group (Group B) received standard postoperative care.

All patients received a standardized postoperative care protocol. Analgesia consisted of intravenous morphine administered at 2 mg for patients weighing < 50 kg or 3 mg for those weighing ≥ 50 kg every 4 hours during the first 24 hours, followed by the same dosing on an as-needed basis on postoperative day 2 (maximum 18 mg/day). Scheduled adjunct analgesics included oral paracetamol 500 mg every 6 hours on postoperative days 1 and 2, and oral ibuprofen 400 mg after meals on postoperative days 1 and 2, except in cases of severe dyspepsia, chronic kidney disease, or non-steroidal anti-inflammatory drugs allergy. Prokinetic therapy consisted of intravenous metoclopramide 10 mg administered every 8 hours during the first 24 hours, and subsequently on an as-needed basis on postoperative day 2, with a maximum total dose of 30 mg/day. Requests for additional morphine were recorded as part of the secondary outcome assessing supplemental analgesia, and requests for additional metoclopramide were documented as a secondary outcome evaluating the need for additional antiemetics. A postoperative protocol was prepared for all patients using the same doctor's standing postoperative order. Intravenous fluid was replaced during the first 24 hours after surgery at a maintenance rate using the Holliday-Segar calculator, and early ambulation was undertaken on the day following surgery. The removal of a urinary catheter was done on the first operating morning. A postoperative feeding regimen, which included 30-60 mL of water, clear liquids, and a soft diet, was permitted on the first postoperative day or as tolerated by the patients.

A regular diet was added on the second postoperative day.

After patients regained full consciousness, ward staff (physicians or nurses) who had been instructed on the standardized documentation protocol obtained the outcome information directly from the patients and recorded it in the medical records. The primary outcome, time to first passage of flatus, was defined as the interval from the end of surgery to the patient-reported first passage of gas. Staff were trained to verify each report and document the exact time using the central digital ward clock to ensure consistency. The secondary outcomes were the duration from the end of surgery to first defecation, postoperative nausea, postoperative vomiting, additional analgesics, and antiemetic drugs.

Adverse effects of xylitol and mint, including hives, rash, dizziness, nausea, vomiting, and difficulty breathing, were observed by ward staff. In the event of an adverse effect, the doctor assessed the symptoms and determined the appropriate treatment. The symptoms were closely monitored until improvement.

The patient was discharged after all required conditions were accomplished, including stable vital signs and no fever for at least 24 hours, solid diet tolerance, regular urination, passing flatus, no vaginal bleeding or abdominal pain, absence of any complication from the operations, and the ability to ambulate without assistance. The first-time defecation was collected, or was requested via telephone on the third day after discharge, if the patient had not passed stool during the hospital stay.

The sample size calculation was based on a pilot study involving 15 women per group. The mean time to first flatus in the chewing gum group was 33.3 hours with a standard deviation (SD) of 14.2 hours. In contrast, the control group was 41.6 hours with a SD of 11.2 hours. The sample size was calculated using the formula for the difference between two independent means, with a one-sided alpha error of 5%, a power of 80%, and a 10% dropout rate. This required a total of 68 women, with 34 women in each group.

Data were analyzed using the R statistical software, version 4.4.1. Differences in continuous variables were analyzed using student's t-test or the Wilcoxon rank-sum test and were presented as means with standard deviation or median with interquartile range. Categorical variables were analyzed via the chi-square test or Fisher's exact test and presented in percentages. The Kaplan-Meier curve illustrated the difference in time to first flatus and time to first defecation between the gum-chewing group and the control group, as determined by the log-rank test. The p value < 0.05 was considered statistically significant.

Based on the ethical principles of research aimed at protecting human rights, security, and human dignity, this proposal was submitted to Khon Kaen Hospital. Ethical approval was obtained from the Institutional Review Board of Human Research. (reference number: KEF67010). The study has been registered at the Thai Clinical Trials Registry (TCTR20240730002)).

Results

From July 2024 to March 2025, 115 eligible women with gynecologic malignancies who underwent surgical staging were enrolled in the study. Forty-seven were excluded from the analysis as 44 did not meet the inclusion criteria and three refused to participate. Sixty-eight eligible women were randomly assigned to two groups at a ratio of 1:1. There were no dropouts in this study. Thirty-four participants from two groups were analyzed (Fig.1).

Baseline characteristics showed no statistical difference between the chewing gum group and those who received standard postoperative care in terms of age, body mass index, underlying diseases, type of cancer, International Federation of Gynaecology and Obstetrics stage of cancer, incision, operation time, estimated blood loss, and blood transfusion, as well as frequency (Table 1). The most common diagnosis was endometrial cancer. And the participants were mainly at an early stage.

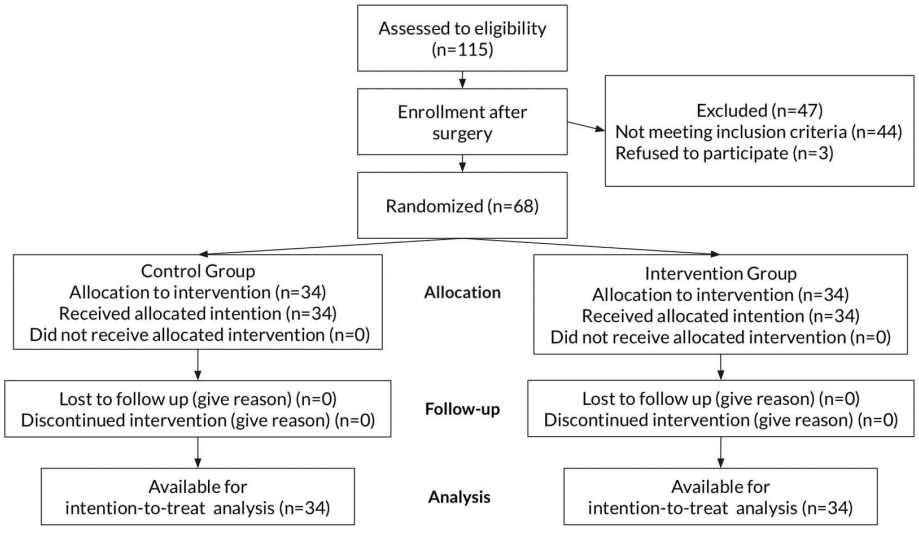

Fig. 1. Consort flow diagram.

Table 1. Demographic characteristics.

Demographic Profiles	Intervention group (n = 34) mean ± SD or n (%)	Control group (n = 34) mean ± SD or n (%)	p value
Age (years)	55.4 ± 9.9	56.4 ± 11.2	0.682
BMI (kg/m^2)	24.4 ± 5.8	26 ± 5.3	0.241
Underlying diseases, n (%)	14 (41.2)	21 (61.8)	0.145
Hypertension	8 (23.5)	15 (44.1)	0.124
Diabetes mellitus	5 (14.7)	7 (20.6)	0.750
Cardiovascular disease	2 (5.9)	0 (0)	0.493
Others	6 (17.6)	8 (23.5)	0.764
Type of cancers, n (%)			
Ovarian cancer	9 (26.5)	4 (11.8)	0.217
Endometrial cancer	17 (50)	24 (70.6)	0.137
Others	8 (23.5)	6 (17.6)	0.764
FIGO stage of cancer, n (%)			
Early stage (I-II)	19 (70.4)	17 (56.7)	0.426
Advanced stage (III-IV)	8 (29.6)	12 (40)	0.588
Previous abdominal surgery n (%)	21 (61.8)	24 (70.6)	0.608
Incision, n (%)			
Low midline	27 (79.4)	28 (82.4)	1.000
Pfannenstiel	6 (17.6)	3 (8.8)	0.476
Maylard	1 (2.9)	3 (8.8)	0.614
Operation time (mins)	124.1 ± 24.4	118.9 ± 31.7	0.448
EBL (mL), median (IQR)	200 (100, 200)	200 (100, 300)	0.975
Blood transfusion, n (%)	3 (8.8)	1 (2.9)	0.614

SD: standard deviation, BMI: body mass index, EBL: estimated blood loss, IQR: interquartile range, FIGO: International Federation of Gynaecology and Obstetrics.

The time to first flatus was 33.5 ± 11.7 hours and 42.7 ± 11.7 hours in the gum chewing group and those who received routine standard postoperative care, respectively. The mean difference was -9.2 hours (95%CI -14.9 to -3.6). The time to first flatus was significantly shorter in the gum chewing group compared to the control group (p = 0.002) (Table 2).

Furthermore, the use of additional antiemetics was 8.8% in the gum chewing group and 32.4% in the control group (Table 3). The relative risk was 0.3, with a p value of 0.036, indicating a statistically significant reduction in the gum chewing group compared to the control group.

Kaplan-Meier curves of time to first flatus and time to first defecation were analyzed as time-to-event (Fig. 2, 3). No significant difference was observed in terms of time to first defecation, postoperative nausea, postoperative vomiting, and additional analgesic use. No serious adverse effects from chewing gum were reported in this study.

Table 2. Primary outcome.

Primary outcome	Intervention group (n = 34) mean ± SD	Control group (n = 34) mean ± SD	mean difference	95%CI	p value
Time to first flatus (hours)	33.5 ± 11.7	42.7 ± 11.7	-9.2	-14.9, -3.6	0.002

SD: standard deviation, CI: confidence interval

Table 3. Secondary outcomes.

Secondary outcome	Intervention group (n = 34) mean ± SD or n (%)	Control group (n = 34) mean ± SD or n (%)	mean difference	95%CI	p value
Time to first defecation (hours)	50.7 ± 16	56.7 ± 17.3	-5.9	-14.0, 2.2	0.149
Postoperative					
nausea	7 (20.6)	11 (32.4)			0.410
vomiting	2 (5.9)	5 (14.7)			0.427
Additional drugs					
analgesics	4 (11.8)	5 (14.7)			1.000
antiemetics	3 (8.8)	11 (32.4)			0.036

SD: standard deviation, CI: confidence interval

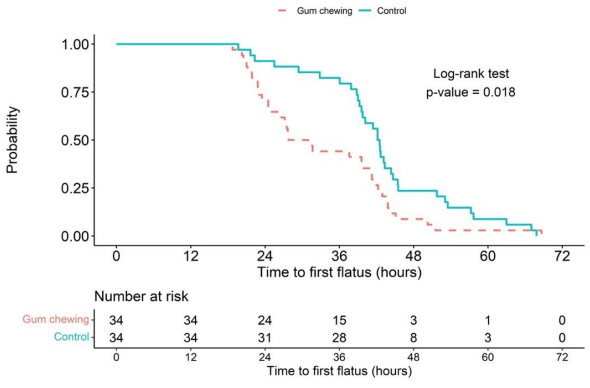

Fig. 2. Time to first flatus (hours).

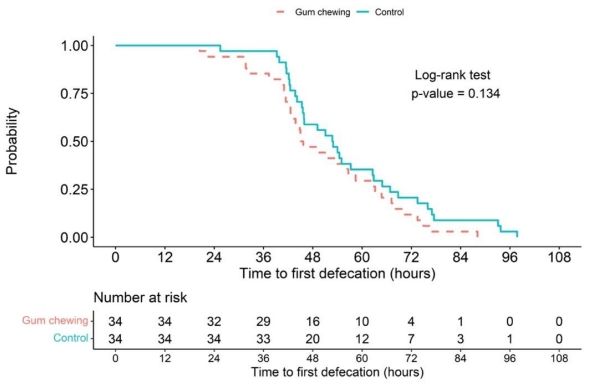

Fig. 3. Time to first defecation (hours).

Discussion

This single-blind randomized controlled trial evaluated the efficacy of postoperative chewing gum on the recovery of gastrointestinal function following complete surgical staging for gynecologic malignancies. The study revealed that time to first flatus in the chewing gum group was significantly shorter than in those who received standard routine postoperative care, with a mean difference of 9.2 hours (33.5 ± 11.7 vs 42.7 ± 11.7 hours, p = 0.002). This supported the theory that sham feeding through gum chewing could activate the cephalic-vagal reflex pathway, thereby enhancing gastrointestinal motility and reducing postoperative ileus.

Our findings were consistent with several prior studies conducted in complete surgical staging of gynecologic malignancies. For example, Ertas et al[19] conducted a randomized trial in patients undergoing complete surgical staging in gynecologic malignancies. They reported that chewing gum showed a significantly shorter time to flatus and bowel movement compared to standard care. Their time to first flatus aligned closely with our primary outcome. Correspondingly, Arphamart et al[20] studied women who underwent gynecologic cancer surgeries in laparotomy and laparoscopic surgeries. They found that chewing gum reduced the time to first flatus. In both studies, as in ours, chewing gum was a low-cost, safe intervention with minimal risk and clinical benefit.

The methodology regarding gum chewing, including the initiation timing, duration, frequency, and amount, varied compared to other studies. In our research, gum chewing was initiated on the first postoperative morning and continued for 15 minutes, 4 times per day, until the first passage of flatus. On the contrary, a systematic review of randomized controlled trials by Yin et al[21], studying the impact of gum chewing on postoperative bowel ileus following gynecological cancer surgery, reported that all studies related to complete surgical staging applied a longer chewing duration, typically 30 minutes, three times per day. Although the gum chewing duration of our study was shorter, the time to first flatus result was similar to that of Ertas et al[19], who used a 30-minute chewing protocol. Correspondingly, a study by Nanthawong et al[22] on gum chewing in benign gynecologic surgery using a 15-minute protocol also showed that gum chewing can shorten the time to first flatus, indicating early recovery of gastrointestinal function. Although complete surgical staging was more complex and the duration was longer, our outcomes were similar to those observed in the benign study. This suggested that a 15-minute protocol could maintain therapeutic efficacy and minimize side effects and discomfort symptoms, such as jaw pain and dry mouth, associated with chewing gum.

While the primary outcome demonstrated a clear benefit, the effect of chewing gum on secondary outcomes was more variable. Although the time to first defecation was shorter in the intervention group (50.7 ± 16.0 vs 56.7 ± 17.3 hours), this difference was not statistically significant (p = 0.149), similar to that of Arphamart et al[20]. The result may have been affected by additional factors, such as individual bowel habits, hydration status, opioid use, and perioperative diet tolerance[23], which may cause results to differ from our initial expectations.

In addition, our study found a significantly lower rate of additional antiemetic use in the gum-chewing group (8.8% vs 32.4%, p = 0.036), despite no statistically significant differences in nausea and vomiting rates. This finding suggested that gum chewing may relieve discomfort or mild gastrointestinal symptoms that do not meet the threshold for diagnosis but still impact recovery. No statistically significant differences were found in postoperative nausea, vomiting, or analgesic use in this study. However, these outcomes had a relatively low incidence in both groups, possibly limiting the ability to detect meaningful differences. Moreover, the absence of adverse effects associated with chewing gum across our research supports its safety, consistent with Yin et al[21] and Arphamart et al[20].

The strength of this study was its randomized controlled design. This research had a specific focus

on patients undergoing complete surgical staging. There were no dropouts.

Due to the limited time for data collection, a limitation of this study was the lack of data on quality of life outcomes, which are key indicators of recovery in ERAS protocols. While Short et al[24] reported reduced hospital stays with chewing gum in general surgical populations, our study did not collect this data. Future research in gynecologic oncology should investigate these data to assess the intervention's impact more comprehensively.

According to the ERAS guidelines for gynecologic oncology surgery, the use of chewing gum was recommended, albeit with a weak endorsement. From our perspectives, chewing gum could be a simple, non-invasive, and cost-effective addition to postoperative care for patients undergoing complete surgical staging. It might offer clinical benefits to these patients.

This study population mainly consisted of women with early-stage disease. Future research should focus on multicenter studies involving patients with various types of gynecologic cancers and different levels of surgical complexity. Adjuncts to other modalities in the ERAS protocol, such as early feeding, opioid-sparing analgesia, and early ambulation, might prove beneficial and warrant further investigation.

Conclusion

In summary, chewing gum significantly encouraged the return of gastrointestinal function after complete surgical staging for gynecologic malignancies. No significant adverse effects were reported, supporting its safe use in postoperative care.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Effects of Intramuscular Pethidine on Labor Duration: A Prospective Cohort Study

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ABSTRACT

Objectives: This study evaluated the impact of intramuscular pethidine on labor duration as well as associated maternal and neonatal outcomes.

Materials and Methods: A prospective cohort study at Hatyai Hospital recruited 114 women with singleton, cephalic pregnancies at 37–41 weeks and spontaneous labor in the active phase from May to December 2024. A total of 59 patients chose to receive intramuscular pethidine at a dose of 1 mg/kg, while 41 patients chose not to receive it. Obstetric outcomes, labor characteristics, pain assessment by visual analog scale, and maternal and neonatal drug adverse outcomes were recorded. Multivariable linear regression identified factors associated with labor duration, adjusting for confounders including maternal age, body mass index (BMI), and parity.

Results: The median duration of the active phase of the first stage of labor was significantly shorter in the pethidine group (165 min [interquartile range (IQR) 110, 245]) compared to the non-pethidine group (220 min [IQR 140, 330], p = 0.046). After adjusting for maternal age, BMI, and parity, pethidine administration was found to be associated with a significant reduction in active phase duration by 67.45 minutes (adjusted coefficient = -67.45, 95% confidence interval -118.67, -16.23, p = 0.010). None of birth asphyxia was reported, and no significant differences was observed in neonatal intensive care unit admission. Mild maternal side effects included drowsiness and nausea in the pethidine group, but no severe adverse effects were observed in either group.

Conclusion: Intramuscular pethidine administration significantly shortened the active phase of the first stage of labor compared to the non-pethidine group after adjusting for confounding factors, without increasing adverse maternal or neonatal outcomes.

Keywords: pethidine, intramuscular analgesia, labor duration, obstetric outcomes, neonatal outcomes, pregnancy.

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ผลของเพทิดีนแบบฉีดเข้ากล้ามเนื้อต่อระยะเวลาการคลอด: การศึกษาแบบติดตามไปข้างหน้า

กันตพงศ์ ไพบูลย์ศิริจิต, พักตร์ประภา ไชยภักดี

บทคัดย่อ

วัตถุประสงค์: *การศึกษานี้ประเมินผลกระทบของเพทิดีนแบบฉีดเข้ากล้ามเนื้อต่อระยะเวลาการคลอดและผลลัพธ์ที่เกี่ยวข้องต่อมารดาและทารกแรกเกิด*

วัสดุและวิธีการ: *การศึกษาแบบติดตามไปข้างหน้าที่โรงพยาบาลหาดใหญ่ได้คัดเลือกหญิงตั้งครรภ์ 114 คนที่เป็นครรภ์เดี่ยว ทารกในครรภ์มีศีรษะเป็นส่วนนำ อายุครรภ์ 37-41 สัปดาห์ และมีการเจ็บครรภ์คลอดเองในระยะ active phase ตั้งแต่เดือนพฤษภาคมถึงธันวาคม 2567 มีผู้ป่วย 59 รายเลือกที่จะรับเพทิดีนแบบฉีดเข้ากล้ามเนื้อในขนาด 1 มก./กก. ขณะที่ผู้ป่วย 41 รายเลือกที่จะไม่รับยา มีการบันทึกผลลัพธ์ทางสูติกรรม ลักษณะการคลอด การประเมินความเจ็บปวดโดยใช้มาตรวัดแบบภาพเปรียบเทียบความเจ็บปวด และผลข้างเคียงของยาต่อมารดาและทารกแรกเกิด การวิเคราะห์ถดถอยเชิงเส้นแบบหลายตัวแปรใช้ระบุปัจจัยที่เกี่ยวข้องกับระยะเวลาการคลอด โดยมีการปรับค่าสำหรับตัวแปรกวน ได้แก่อายุมารดา ดัชนีมวลกาย และจำนวนครั้งที่เคยคลอด เป็นต้น*

ผลการศึกษา: *ค่ามัธยฐานของระยะเวลาในช่วง active phase ของระยะคลอดที่หนึ่งสั้นกว่าอย่างมีนัยสำคัญในกลุ่มที่ได้รับเพทิดีน (165 นาที [interquartile range (IQR) 110, 245]) เมื่อเทียบกับกลุ่มที่ไม่ได้รับเพทิดีน (220 นาที [IQR 140, 330], p = 0.046) หลังจากปรับสำหรับอายุมารดา ดัชนีมวลกาย และจำนวนครั้งที่เคยคลอด การให้เพทิดีนสัมพันธ์กับการลดลงอย่างมีนัยสำคัญของระยะเวลาในช่วง active phase 67.45 นาที (ค่าสัมประสิทธิ์ที่ปรับแล้ว = -67.45, 95% confidence interval -118.67, -16.23, p = 0.010) ไม่พบภาวะทารกขาดออกซิเจนแรกเกิด รวมถึงอัตราการเข้ารับการรักษาของทารกในหอผู้ป่วยวิกฤตทารกแรกเกิดไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างสองกลุ่ม ผลข้างเคียงที่พบในมารดามีความรุนแรงเล็กน้อย ได้แก่ อาการง่วงซึมและคลื่นไส้ โดยไม่มีรายงานผลข้างเคียงรุนแรงแต่อย่างใด*

สรุป: *การฉีดยาเพทิดีนเข้ากล้ามเนื้อช่วยลดระยะ active phase ของการเจ็บครรภ์คลอดได้อย่างมีนัยสำคัญเมื่อเปรียบเทียบกับกลุ่มที่ไม่ได้รับยา หลังจากได้มีการปรับแก้ผลกระทบของปัจจัยกวนต่างๆ แล้ว โดยไม่เพิ่มอัตราการเกิดผลแทรกซ้อนในมารดาและทารก*

คำสำคัญ: *เพทิดีน, ยาระงับปวดทางกล้ามเนื้อ, ระยะเวลาการคลอด, ผลลัพธ์ทางสูติศาสตร์, ผลลัพธ์ทางทารกแรกเกิด, การตั้งครรภ์*

Introduction

Labor is a critical physiological process that is accompanied by intense pain and marked variability in duration, both features can profoundly affect maternal and neonatal outcomes. The length of labor is influenced by multiple factors, including parity, uterine contractility, fetal weight, and maternal stress levels[1-2]. When labor is prolonged, particularly during the active phase of the first stage, the risks of maternal exhaustion, operative or instrumental delivery, postpartum morbidity, and adverse neonatal outcomes increase substantially[3]. Accordingly, achieving effective pain control and avoiding unnecessary prolongation of labor are not only issues of maternal comfort but key determinants of safe obstetric care, with direct implications for labor progression and the prevention of maternal and perinatal complications[4].

A wide range of options is available for intrapartum pain control, including non-pharmacologic and pharmacologic strategies. Non-pharmacologic approaches such as continuous labor support, hydrotherapy, position changes, breathing techniques, acupuncture, massage, and transcutaneous electrical nerve stimulation aim to improve women's ability to cope with labor pain while allowing them to remain mobile and avoid unnecessary medical interventions. Pharmacologic methods are broadly categorized into inhalational agents, systemic opioids, and regional analgesia. Nitrous oxide/oxygen provides rapid, self-administered analgesia, whereas epidural and combined spinal/epidural techniques are regarded as the most effective options. However, these require anesthetic expertise and substantial resources that are often unavailable in low-resource settings. Consequently, systemic opioids such as pethidine, morphine, fentanyl, and remifentanil remain widely used because they are familiar to clinicians and can be administered quickly and easily where anesthetic capacity is limited[5]. Pethidine's main mechanism is acting primarily on mu-opioid receptors in the central nervous system. Pethidine effectively reduces pain perception and may enhance uterine contractility by alleviating stress-mediated inhibition of oxytocin release[6-7].

Previous studies have documented the analgesic efficacy and labor-shortening duration of pethidine[7–10]. However, such studies vary widely in their assessment of dosage, administration route, timing of pethidine administration, and type of labor augmentation, and evidence regarding its effect on labor progression remains controversial. In addition, there are limited studies in Thailand specifically investigating its primary effect on shortening labor duration. Furthermore, given the high prevalence of pethidine use in the labor room at Hatyai Hospital, where the usage rate reaches 30%, it is essential to assess its safety because of concerns about its potential impact on maternal and neonatal outcomes, such as hypotension and respiratory depression. Therefore, this study aimed to evaluate the impact of intramuscular pethidine on the duration of the active phase of the first stage of labor, along with pain relief and associated maternal and neonatal outcomes.

Materials and Methods

This prospective cohort study was conducted in the labor room at the Department of Obstetrics and Gynecology, Hatyai Hospital, between May 2024 and December 2024. A prospective cohort design was conducted instead of a randomized controlled trial because intrapartum analgesia at Hatyai Hospital is determined by patient request. Random allocation of pethidine would have required overriding patients' choices regarding analgesia, which was considered ethically unacceptable under institutional review board standards and incompatible with respect for patient autonomy. Approval for this research was obtained from the Institutional Review Board of Hatyai Hospital (IRB: HYH-EC 119-66-01) on April 1, 2024. Pregnant women aged 18-40 years, with singleton pregnancies at gestational ages of 37-41 weeks, were recruited. Inclusion criteria included spontaneous labor onset, cervical dilation of 4 cm at admission, a vertex fetal presentation, and good uterine contraction. Exclusion criteria included all high-risk pregnancies,

such as preeclampsia, gestational diabetes, placenta previa, fetal growth restriction, fetal malpresentation, and previous cesarean deliveries.

The sample size was determined using G*Power 3.1. The expected effect size was derived from Yilmaz et al[11]. Based on the reported mean difference and pooled standard deviation in that study, a standardized mean difference of Cohen's d = 0.57 was obtained. For a two-independent-means comparison with an unequal allocation ratio (N_2/N_1 = 1.39) cited from intrapartum analgesia utilization in Hatyai Hospital's Labor unit throughout 2023, 100 participants (n_1 = 42 and n_2 = 58) were required to achieve 80% power at a two-sided $\alpha = 0.05$. Allowing for an anticipated 14% dropout rate due to emergency cesarean delivery or instrumental delivery, the final sample size was 114 participants.

After informed consent was obtained, baseline demographic data were collected, including maternal age, parity, and body mass index (BMI), and vaginal examination was performed. Labor progress was monitored using standard partographic methods. When cervical dilatation reached 4 cm, pain assessment by visual analog scale (VAS) was recorded at 0, 1, and 2 hours. If uterine contractions were inadequate, augmentation was performed at the physician's discretion. Augmentation methods, based on Hatyai Hospital's standard labor management protocol, included amniotomy, oxytocin infusion, or a combination of both. Oxytocin infusion started at 4 milliunits per minute and was increased by 3-6 milliunits per minute every 15-40 minutes as managed by a registered nurse. The initiation time and dosage of oxytocin (in milliunits per minute) were recorded systematically, along with subsequent dosage adjustments made following established labor room protocols. Uterine contractions were documented at each dosage adjustment, including duration, interval, and Montevideo units. If augmentation was performed using amniotomy, the procedure time was recorded, and cervical assessment, amniotic fluid characteristics, and contraction patterns were documented.

According to Hatyai Hospital's labor room protocol, intrapartum analgesia is provided strictly on a patient-request basis. Participants who requested analgesia, provided that cervical dilation had not exceeded 6 cm, were placed in the pethidine group and received pethidine 1 mg/kg intramuscular. Those who declined analgesia were placed in the non-pethidine group. No randomization or investigator-directed allocation occurred. VAS was reassessed at 0, 1, and 2 hours after drug administration. Before and after pethidine administration, vital signs were recorded at 0, 30, and 60 minutes. Electronic fetal heart rate monitoring was conducted continuously during the intrapartum period, with pelvic examinations performed every 2 hours to assess labor progression.

The primary outcome was the duration of the active phase of the first stage of labor. The duration of the active phase of the first stage of labor was defined for each participant as the time from cervical dilatation of 4 cm with adequate uterine contractions to full dilatation at 10 cm. The secondary outcomes included VAS assessments conducted before and at 1 and 2 hours after pethidine administration, maternal complications such as maternal bradycardia (pulse rate < 60 bpm), hypotension (systolic blood pressure < 100 mmHg or a reduction of ≥ 20% from baseline), nausea-vomiting, deoxygenation (oxygen saturation < 95%) and respiratory depression (respiratory rate < 8 breaths per minute). Neonatal complications assessed were birth asphyxia (APGAR score < 7 at 1 and 5 minutes), neonatal intensive care unit (NICU) admissions, and neonatal latch, audible swallowing, type of nipple, comfort and hold (LATCH) score less than 6 at 8, 16, 24, and 48 hours post-delivery.

All statistical analyses were performed using R software, version 4.2.1, to ensure precision and reproducibility. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) and compared using independent samples t-tests or Mann–Whitney U tests, as appropriate. Categorical variables were analyzed using chi-square tests or Fisher's exact tests. To identify factors associated with the duration

of the active phase of the first stage of labor, univariable linear regression analysis was performed initially. Subsequently, multivariable linear regression analysis was conducted to identify factors independently associated with active phase duration. The covariates included in the multivariable model were maternal age (≤ 18 and ≥ 35 years), parity (nulliparous vs multiparous), BMI (≥ 30 vs < 30 kg/m²), type of labor augmentation, upright position during labor, and intramuscular pethidine injection (yes vs no), all of which have been identified in previous studies as important determinants of labor progression and first stage duration (12-14). Results were presented as crude and adjusted coefficients with 95% confidence intervals (CI), and a p value < 0.05 was considered statistically significant.

Results

During the study period, 1,452 women entered the active phase of labor in the labor unit. Of these, 1,338 did not meet the inclusion criteria and declined to participate, and 114 eligible women were enrolled in the study. Based on their choice to receive or not receive pethidine for analgesia, 66 were allocated to the pethidine group and 48 to the non-pethidine group. However, 7 participants were excluded from the pethidine group; 6 underwent cesarean delivery due to non-reassuring fetal status (n = 1), cephalopelvic disproportion (n = 5), and 1 underwent instrumental delivery due to non-reassuring fetal status. In the non-pethidine group, 7 participants were excluded; 5 participants underwent cesarean delivery due to non-reassuring fetal status (n = 2) and cephalopelvic disproportion (n = 3), and 2 participants underwent instrumental delivery due to non-reassuring fetal status. Ultimately, 100 participants remained in the final analysis, with 59 in the pethidine group and 41 in the non-pethidine group (Fig. 1).

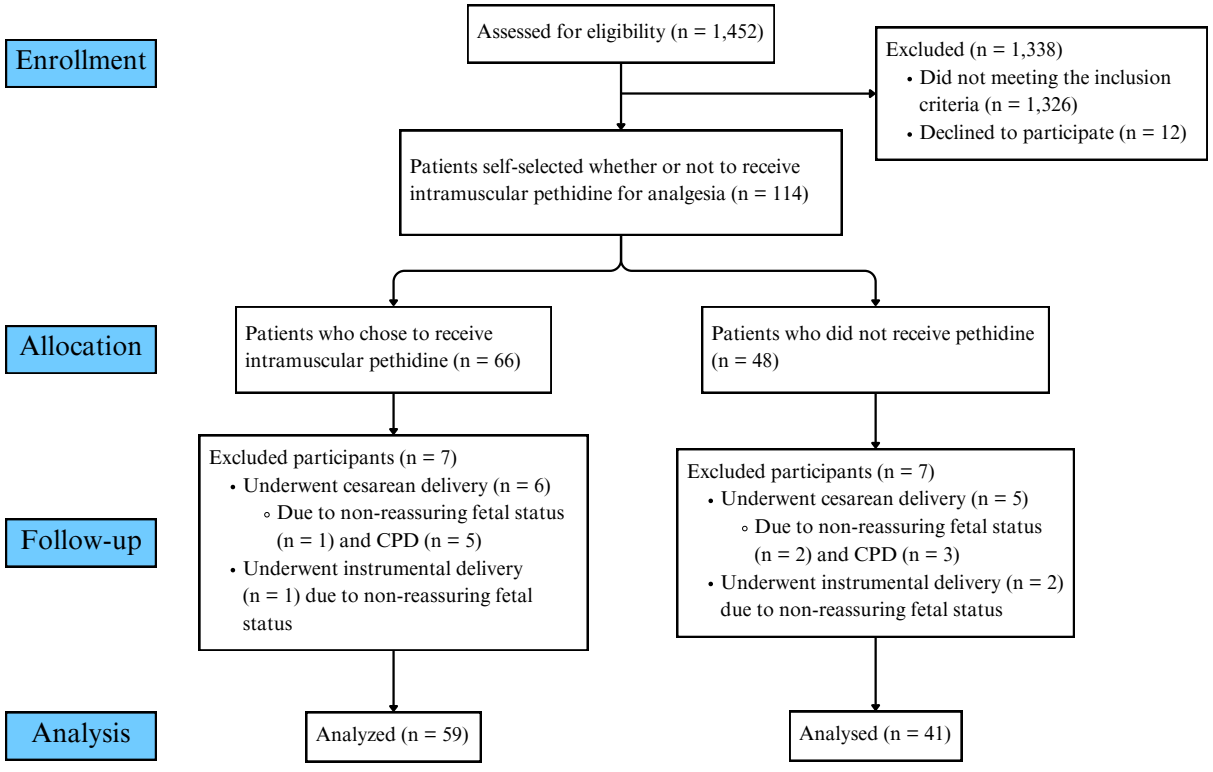

Fig. 1. CONSORT flow diagram of participants recruitment.

The baseline characteristics of the study population revealed no significant differences between the pethidine and non-pethidine groups regarding maternal age (27.3 ± 5.8 vs 26.7 ± 7.1 years, p = 0.655), parity (nulliparous: 54.2% vs 46.3%, p = 0.566), BMI (26.9 vs 26.2 kg/m2, p = 0.710), gestational age (39.4 ± 0.9 vs 39.1 ± 1.0 weeks, p = 0.066) and birth weight (3,047.8 ± 334.1 vs 3,107.8 ± 366.7 grams, p = 0.398). The rate of amniotomy was similar between the groups, with a comparable proportion of patients undergoing this procedure. Additionally, the median VAS score during the active phase was significantly higher in the pethidine group before administration. Oxytocin augmentation was also comparable between the groups, indicating that labor-management approaches were similar across study arms. These findings are detailed in Table 1.

Table 1. Comparison of demographics and obstetric outcomes between participants receiving or not receiving pethidine.

	Overall (n = 100)	Pethidine (n = 59)	Non-pethidine (n = 41)	p value*
Age (years), mean ± SD	27 ± 6.4	27.3 ± 5.8	26.7 ± 7.1	0.655[t]
Gestational age (weeks), mean ± SD	39.3 ± 1.0	39.4 ± 0.9	39.1 ± 1.0	0.066[t]
BMI (kg/m^2), median (IQR)	26.8 (23.7, 30.1)	26.9 (23.9, 29.9)	26.2 (23.4, 30.2)	0.710[m]
BMI (kg/m^2)				1.000[c]
< 30 (%)	74 (74.0)	44 (74.6)	30 (73.2)	
≥ 30 (%)	26 (26)	15 (25.4)	11 (26.8)	
Parity				0.566[c]
Nulliparous (%)	51 (51.0)	32 (54.2)	19 (46.3)	
Multiparous (%)	49 (49.0)	27 (45.8)	22 (53.7)	
VAS at active phase, median (IQR)	7 (5.0, 8.0)	8 (6.0, 10.0)	6 (4.0, 7.0)	< 0.001[m]
Augmentation				0.445[f]
Amniotomy only (%)	8 (11.8)	6 (14.3)	2 (7.7)	
Oxytocin only (%)	40 (58.8)	22 (52.4)	18 (69.2)	
Amniotomy + Oxytocin (%)	20 (29.4)	14 (33.3)	6 (23.1)	
Birth weight (grams), mean ± SD	3,072.4 ± 346.0	3,047.8 ± 334.1	3,107.8 ± 366.7	0.398[t]

SD: standard deviation, BMI: body mass index, VAS: visual analog scale, IQR: interquartile range
Data are presented as n (%), mean ± SD, or median (IQR).
p value corresponds to t = independent samples t-test, c = chi-square test, m = Mann-Whitney U test, f = Fisher's exact test. * significant at p value < 0.05

Notably, the active phase of labor was shorter in the pethidine group, with a median duration of 165 minutes (IQR 110, 245) compared to 220 minutes (IQR 140, 330) in the control group (p = 0.046), demonstrating a significant reduction in labor duration. The duration of the second and third stages did not differ significantly between the groups. These findings are detailed in Fig. 2.

Maternal side effects were minimal, with drowsiness and nausea being the most frequently reported in the pethidine group (11.8% and 8.5%, respectively). No incidents of hypotension, respiratory distress, or oxygen desaturation were observed. When amniotic fluid was dichotomized as meconium-stained versus clear, meconium was present in 16.9% (10/59) of the pethidine group and 7.3% (3/41) of the non-pethidine group. This difference was not statistically significant (p = 0.23). Neonatal outcomes, including birth asphyxia and desaturation, were comparable across the groups (p > 0.05), although NICU admissions were slightly higher in the pethidine group (n = 5) compared to the non-pethidine group (8.5% vs 2.4%, p = 0.396). Among the five NICU admissions in the pethidine group, two cases were due to early neonatal sepsis, and three cases were attributed to transient tachypnea of the newborn, indicating that the observed increase in NICU

admissions was not associated with pethidine-induced respiratory depression. Additionally, LATCH scores at 8, 16, 24, and 48 hours postdelivery did not differ significantly between the groups, indicating pethidine had no observed impact on the success of early breastfeeding. These findings are detailed in Table 2.

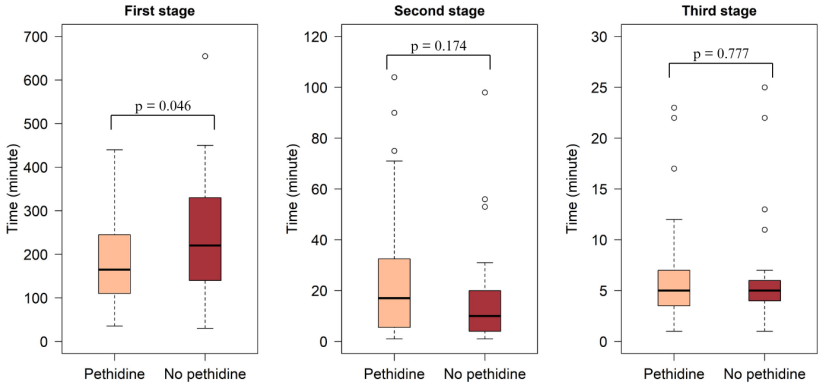

Fig. 2. Comparison of median duration in the active phase of the first, second, and third stages of labor between participants receiving and not receiving intramuscular pethidine.

Table 2. Comparison of obstetric outcomes, maternal adverse drug effects, and neonatal outcomes between participants receiving and not receiving intramuscular pethidine.

	Pethidine (n = 59)	Non-pethidine (n = 41)	p value
Maternal adverse drug effect (%)			
Drowsiness	7 (11.8%)	-	
Nausea vomiting	5 (8.5%)	-	
Dizziness	2 (3.4%)	-	
Meconium-stained amniotic fluid (%)			0.229[f]
Present	10 (16.9)	3 (7.3)	
Absent	49 (83.1)	38 (92.7)	
Fetal heart rate pattern (%)			0.351[f]
CAT 1	54 (91.5)	35 (85.4)	
CAT 2	5 (8.5)	6 (14.6)	
Birth weight (grams), mean ± SD	3,047.8 ± 334.1	3,107.8 ± 366.7	0.398[t]
APGAR score, median (IQR)			
1 min	9 (9,9)	9 (9,9)	0.092[m]
5 min	9 (9,9)	9 (9,9)	0.242[m]
NICU admission (%)	5 (8.5)	1 (2.4)	0.396[f]
Neonatal desaturation (%)	3 (5.1)	3 (7.3)	0.687[f]
LATCH score, median (IQR)	3 (5.1)	3 (7.3)	0.687[f]
At 8 hours	8 (8.0, 9.0)	8 (8.0, 9.0)	0.818[m]
At 16 hours	8 (8.0, 9.0)	8 (8.0, 9.0)	0.979[m]
At 24 hours	8 (8.0, 9.0)	8 (8.0, 9.0)	0.975[m]
At 48 hours	8 (8.0, 9.0)	8 (8.0, 9.0)	0.992[m]

CAT: category of electronic fetal monitoring by the National Institute of Child Health and Human Development (NICHD), LATCH: latch, audible swallowing, type of nipple, comfort, and hold.
Present meconium includes both thin and thick meconium, absent indicates clear amniotic fluid. p value corresponds to m = Mann-Whitney U test, f = Fisher's exact test, or t = independent samples t-test.

The study results indicated that the initial VAS scores were significantly higher in the pethidine group before administration (median 8, IQR 6, 10) compared to the non-pethidine group (median 6, IQR 4, 7) ($p < 0.001$), reflecting the fact that women with more severe pain were more likely to request intramuscular pethidine for pain relief. Median VAS scores before and 1 hour after pethidine administration were 8 (IQR 7, 10) vs 8 (IQR, 7, 10) ($p = 0.109$). It showed that, although some patients experienced pain relief, the overall median pain score did not show a statistically significant reduction post-administration. Subsequently, median VAS scores increased significantly from 8 (IQR 7, 10) to 9 (IQR 8, 10) ($p = 0.004$) between 1 and 2 hours after injection. When comparing the initial VAS scores with those at 2 hours, the change from 8 (IQR 6, 10) to 9 (IQR 8, 10) did not reach statistical significance ($p = 0.724$). These temporal changes in pain scores in the pethidine group are illustrated in Fig. 3.

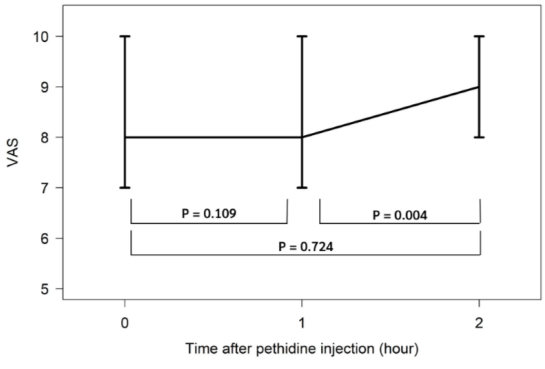

Fig. 3. Changes in visual analog scale (VAS) scores before and after pethidine administration.

In the multivariable linear regression model, maternal age, parity, BMI, type of labor augmentation, upright position during labor, and intramuscular pethidine injection were included as potential determinants of active phase duration. Maternal age was not significantly associated with the duration of the active phase, with non-significant coefficients both for women aged ≤ 18 years (–91.59 minutes; 95% CI –184.36, 1.19; $p = 0.053$) and for those aged ≥ 35 years (–48.11 minutes; 95% CI –120.18, 23.96; $p = 0.188$). Multiparity and obesity (BMI ≥ 30 kg/m^2) were not significantly associated with the duration of the active phase (adjusted coefficients –23.71 minutes; 95% CI –76.59, 29.16; $p = 0.375$ and 2.65 minutes; 95% CI –52.38, 57.68; $p = 0.924$, respectively) (Table 4). Therefore, the coefficients represent mean differences in active phase duration compared with the reference categories, with positive values indicating longer and negative values indicating shorter duration.

Similarly, the method of labor augmentation (amniotomy only, oxytocin only, or amniotomy and oxytocin) and upright position did not significantly influence active phase duration (adjusted coefficient 46.50 minutes; 95% CI –2.48, 95.49; $p = 0.063$). In contrast, intramuscular pethidine injection remained an independent predictor of a shorter active phase when compared with non-pethidine management, with an adjusted coefficient of –67.45 minutes (95% CI –118.67, –16.23; $p = 0.010$), corresponding to a reduction of approximately 67 minutes in the active phase after adjustment for all other covariates (Table 3).

In the pethidine group (n = 59), most women received a dose of 50 mg (31 women, 52.5%), followed by 75 mg (26 women, 44.1%) and 100 mg (2 women, 3.4%). The mean weight-adjusted dose was 0.92 ± 0.17 mg/kg per dose. The median interval from pethidine administration to delivery was 139 minutes (IQR 90.8, 221.0), and cervical

dilatation at the time of injection had a median of 4 cm (IQR 4, 5), indicating that pethidine was typically administered in the early active phase of labor (Table 4).

Table 3. Univariable and multivariable linear regression identifying factors associated with the duration of the active phase of the first stage of labor.

	Crude Coeff. (95% CI)	p value	Adjusted Coeff. (95% CI)	p value
Maternal age*		0.410		0.082
≤ 18	-41.91 (-123.78, 39.97)	0.312	-91.59 (-184.36, 1.19)	0.053
≥ 35	-33.15 (-98.77, 32.47)	0.319	-48.11 (-120.18, 23.96)	0.188
Multiparity	-13.33 (-59.89, 33.24)	0.571	-23.71 (-76.59, 29.16)	0.375
BMI ≥ 30 kg/m^2	-2.05 (-55.21, 51.11)	0.939	2.65 (-52.38, 57.68)	0.924
Augmentation		0.884		0.831
Amniotomy	-9.25 (-102.08, 83.58)	0.844	22.63 (-77.58, 122.83)	0.655
Oxytocin	14.57 (-41.12, 70.27)	0.605	25.43 (-31.85, 82.72)	0.380
Amniotomy and oxytocin	20.5 (-46.44, 87.44)	0.545	25.73 (-58.5, 109.95)	0.545
Upright position	36.05 (-11.44, 83.54)	0.135	46.5 (-2.48, 95.49)	0.063
Pethidine injection	-48.72 (-95.11, -2.33)	0.040	-67.45 (-118.67, -16.23)	0.010

CI: confidence interval, BMI: body mass index

Crude Coeff. (β): crude regression coefficient from univariable linear regression examining each factor individually, Adjusted Coeff. (β): regression coefficient from multivariable linear regression including maternal age, parity, BMI, augmentation method, upright position, and intramuscular pethidine injection.

Table 4. Data on pethidine used in the pethidine group.

	Overall (n = 59)
Pethidine dosage (%)	
50 mg (%)	31 (52.5)
75 mg (%)	26 (44.1)
100 mg (%)	2 (3.4)
MKdose, mean ± SD	0.92 ± 0.17
Pethidine-to-delivery time (minutes), median (IQR)	139 (90.8, 221.0)
Cervical dilatation at pethidine injection, median (IQR)	4 (4, 5)

MKdose: milligrams per kilogram per dose, SD: standard deviation, IQR: interquartile range

Discussion

At Hatyai Hospital, intrapartum analgesia is provided strictly on a patient-request basis, and women demonstrate a strong preference for determining whether they wish to receive pethidine. Enforcing a randomized allocation would require withholding or mandating analgesia against patients' expressed preferences, which directly conflicts with patient autonomy. Such an approach was deemed ethically inappropriate and would not comply with the hospital's IRB standards. Therefore, a prospective cohort design was the only feasible and ethically acceptable design instead of a randomized control trial.

This study examined the impact of intramuscular pethidine on labor duration, with a particular focus on its effect on the active phase of the first stage of labor. Elevated adrenaline levels can inhibit the effectiveness of oxytocin by stimulating β-adrenergic receptors in the uterus, leading to weaker or disorganized contractions[15-16]. By reducing adrenaline, pethidine may indirectly diminish this inhibitory effect, allowing oxytocin to function more efficiently and promote coordinated uterine contractions[11]. The physiological

mechanisms underpinning the efficacy of pethidine in labor progression are multifaceted. Its analgesic properties reduce pain perception and lower circulating catecholamine levels, thereby enhancing uterine contractility and promoting cervical dilation. At the molecular level, pethidine is implicated in enzymatic pathways involving urokinase, plasmin, and collagenase, which facilitate the degradation of cervical collagen[17]. The sedative effects of the drug may also alleviate maternal anxiety, indirectly supporting labor progression[4], reducing maternal anxiety and risk of complications from prolonged labor, such as unrecognized intraamniotic infection in patients with premature rupture of membranes[18]. The findings of this study demonstrated that pethidine administration significantly shortened the duration of the active phase by an average of 67.45 minutes without adversely affecting maternal or neonatal outcomes, similar to previous studies[17, 19-23]. Recent randomized trials from Thailand have shown that other intrapartum interventions can also shorten the active phase of labor, similar to this study, but with different mechanisms. For example, the study by Puttakul et al[24] demonstrated that 5% dextrose in half-strength normal saline infused at 120 mL/h significantly reduced total labor time and the duration of the active phase, as explained by the optimization of myometrial energy supply. Additionally, the study by Kamkong et al[25] similarly reported that a single 20-mg intravenous dose of hyoscine butylbromide shortened the active phase of the first stage of labor due to the reduction of uterocervical spasms. In contrast, other studies reported no significant reduction in labor duration following pethidine administration. This discrepancy may be due to differences in patient selection criteria, labor augmentation methods, pethidine dosage, timing, and administration route[26-27]. These findings emphasized the importance of tailoring pethidine use to individual patients, including patient selection, dosage, timing, and route of administration.

A minimal increase in VAS scores between 1 and 2 hours after pethidine administration was observed, consistent with previous studies[28], indicating that its effectiveness diminishes after 2 hours, although pain should be reduced 1-4 hours after intramuscular pethidine injection using its pharmacological mechanism[29]. However, intramuscular pethidine injection seemingly did not help to reduce VAS pain scores in this study, which can likely be explained by the fact that most women requested pethidine only when their pain was already severe (median VAS 8), so the efficacy of pethidine for their pain relief may be obscured by severe pain during labor progression, thus potentially leaving little margin for a visible numerical decrease in pain score. Moreover, labor pain is highly subjective and influenced by psychological factors, so improvements in uterine activity or stress response may not be fully captured by VAS at fixed time points. In contrast, other studies found that pethidine helped to reduce pain score, which may be due to different baseline pain scores in those populations; the women in those studies had lower pain scores before being given pethidine when compared with this study[22, 30] in higher dosage of pethidine[27, 31], via other routes such as intravenous[26, 32], or with different pain assessment methods[19, 27], which may contribute to patients reporting reduce pain levels. Moreover, pethidine was provided on a patient-request basis. Thus, women who had more severe pain were more likely to request analgesia, resulting in higher baseline VAS scores in the pethidine group. Pethidine can readily cross the placenta and has the potential to induce neonatal respiratory depression, particularly if the neonate is delivered more than 4–5 hours post-administration. Previous research suggests that delivery within 1–4 hours of maternal dosing maintains neonatal pethidine concentrations at levels unlikely to cause significant respiratory suppression[20]. This finding supports the confidence of this study, as the median pethidine-to-delivery time in the cohort was 139 minutes, aligning with the optimal window to mitigate neonatal respiratory risks.

A key strength of this study is that it was one of the few studies from Thailand to examine the

association between intrapartum pethidine and the duration of the active phase of labor. The use of multivariate regression further enhanced the robustness of the findings by adjusting for potential confounders, ensuring a more precise evaluation of the drug's impact. However, the observational nature of the study precluded definitive causal inferences. Additionally, the single-center setting used in this study may limit the generalizability of the findings. While sufficient for primary outcomes, the sample size may not have been large enough to detect rare adverse events. Future multicenter randomized controlled trials are necessary to validate these findings and establish standardized dosing protocols.

Conclusion

Intramuscular administration of pethidine in pregnant women with spontaneous labor in the active phase of the first stage of labor significantly shortened the duration of the active phase by an average of 67.45 minutes compared to the non-pethidine group after adjusting for confounding factors, without increasing obstetric or neonatal risks, and may indirectly alleviate maternal stress related to labor pain.

Acknowledgements

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Modified Word Catheter and Marsupialization in Women with a Cyst or Abscess of the Bartholin Gland: A randomized clinical trial

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ABSTRACT

Objectives: To compare outcomes of a cyst or abscess of the Bartholin gland after surgical treatment using a modified Word catheter or marsupialization.

Materials and Methods: We conducted a single-center, open-label, randomized controlled trial at Vachira Phuket Hospital, in Thailand. Women presenting with a symptomatic Bartholin gland cyst or abscess were randomly assigned to undergo either modified Word catheter placement, using a Foley catheter, or marsupialization under local anesthesia. Participants were followed-up at 1 week, 4 weeks, 6 months, and 12 months post-procedure. The primary outcome was recurrence within one year. Secondary outcomes included procedural time and perioperative pain. Analyses were performed according to the intention-to-treat principle.

Results: A total of 50 women were enrolled between June 2023 and March 2024. Recurrence occurred in 3 of 25 women (12%) in the modified Word catheter group and in 3 of 24 women (12.5%) in the marsupialization group (relative risk 0.96; 95% confidence interval [CI] 0.21, 4.3; $p = 0.957$). The median procedural time was shorter with modified Word catheter placement (10 minutes; interquartile range [IQR] 8, 12) compared to marsupialization (14.5 minutes; IQR 14, 16; $p < 0.001$). Pain scores during the procedure were lower in the modified Word catheter group (mean ± standard deviation [SD] 4.7 ± 1.2) than in the marsupialization group (mean ± SD 6.6 ± 1.1; $p = 0.001$).

Conclusion: In women with a Bartholin gland cyst or abscess, treatment with a modified Word catheter provides similar recurrence rates to marsupialization, but with shorter procedural time and less perioperative pain.

Keywords: Bartholin abscess, Bartholin cyst, word catheter, marsupialization, recurrence.

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การศึกษาเพื่อเปรียบเทียบประสิทธิภาพในการรักษาโรคถุงน้ำหรือฝีต่อมบาร์โธลิน ด้วยการดัดแปลงใช้สายสวนปัสสาวะเลียนแบบสายสวนเวิร์ด กับการผ่าและเย็บปากถุงน้ำ

สุภาพันธ์ วัฒนเจริญ, ชาญชัย สุประสงค์สิน

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบผลของการใช้สายสวนปัสสาวะเลียนแบบสายสวนเวร์ด(modified Word catheter) กับการผ่าและเย็บปากถุงน้ำ (marsupialization)ในการรักษาโรคถุงน้ำหรือฝีต่อมบาร์โธลิน*

วัสดุและวิธีการ: *การศึกษานี้เป็นการทดลองแบบสุ่มที่ดำเนินการ ณ โรงพยาบาลวชิระภูเก็ต ประเทศไทย ในสตรีที่มีถุงน้ำหรือฝีของต่อมบาร์โธลินที่มีอาการ โดยสุ่มได้รับการรักษาด้วยการใส่ Modified Word catheter (ใช้สายสวนปัสสาวะ Foley catheter) หรือการทำ marsupialization ภายใต้การฉีดยาชาเฉพาะที่ มีการติดตามผลที่ 1 สัปดาห์, 4 สัปดาห์, 6 เดือน และ 12 เดือน ผลลัพธ์หลักคือการกลับเป็นซ้ำภายในหนึ่งปี ผลลัพธ์รอง ได้แก่ เวลาในการทำหัตถการและความเจ็บปวดระหว่างและหลังหัตถการ การวิเคราะห์ข้อมูลใช้หลักการ intention-to-treat*

ผลการศึกษา: *มีผู้เข้าร่วมทั้งหมด 50 คน ระหว่างเดือนมิถุนายน 2566 ถึงมีนาคม 2567 การกลับเป็นซ้ำพบใน 3 รายจาก 25 ราย (ร้อยละ 12) ในกลุ่ม Modified Word catheter และ 3 รายจาก 24 ราย (ร้อยละ 12.5) ในกลุ่ม marsupialization (อัตราส่วนความเสี่ยง [RR] 0.96; ช่วงความเชื่อมั่น 95% 0.21, 4.3; p = 0.957) เวลาการทำหัตถการสั้นกว่าชัดเจนในกลุ่ม Modified Word catheter (มัธยฐาน 10 นาที; interquartile range [IQR] 8, 12) เทียบกับ marsupialization (มัธยฐาน 14.5 นาที; IQR 14, 16; p < 0.001) และมีคะแนนความเจ็บปวดขณะทำหัตถการต่ำกว่า (ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน 4.7 ± 1.2 เปรียบเทียบกับ 6.6 ± 1.1; p = 0.001)*

สรุป: *ในสตรีที่มีถุงน้ำหรือฝีของต่อมบาร์โธลิน การรักษาด้วย Modified Word catheter และ marsupialization ให้ผลการกลับเป็นซ้ำใกล้เคียงกัน โดย Modified Word catheter มีข้อได้เปรียบด้านระยะเวลาหัตถการสั้นกว่าและลดความเจ็บปวดได้ดีกว่า*

คำสำคัญ: *ฝีต่อมบาร์โธลิน, ถุงน้ำต่อมบาร์โธลิน, สายสวนเวร์ด, การผ่าและเย็บปากถุงน้ำ, การเกิดเป็นซ้ำ*

Introduction

A cyst of the Bartholin gland is defined as a swelling filled with mucus at the 4 or 8 o'clock position of the vulva vestibule at the position of the duct of the Bartholin gland. If the same swelling is accompanied by signs of infection or inflammation such as redness, swelling, hotness, or tenderness, it is described as an abscess. Bartholin cysts or abscesses are observed in around 2% of women, generally in their reproductive period[1-3]. Both a cyst and an abscess can cause limitation of activity, and an abscess can also cause extreme pain.

Several treatment modalities exist for Bartholin cysts and abscesses, including needle aspiration, incision and drainage, marsupialization, Word catheter placement, and gland excision. Among these, marsupialization and Word catheter insertion are the most commonly employed techniques. Needle aspiration and simple incision and drainage are associated with high recurrence rates (35–45%), whereas gland excision carries a heightened risk of complications, such as hematoma formation, excessive bleeding, external genital deformity, and scarring[2,3]. The primary challenge in managing Bartholin cysts and abscesses is minimizing recurrence following treatment. Comparative studies have reported recurrence rates ranging from 0–13% for marsupialization and 3–17% for Word catheter placement[1, 2, 4-8]. The WoMan trial[9], a multicenter, open-label, randomized controlled study conducted in the Netherlands, found that both procedures had comparable recurrence rates. However, that study demonstrated that Word catheter placement resulted in lower pain scores within the first 24 hours post-treatment and a shorter procedure duration, suggesting potential advantages over marsupialization.

In Thailand, marsupialization remains the standard treatment for Bartholin cysts or abscesses. However, recurrence rates vary across healthcare institutions, often depending on surgical expertise. Higher recurrence rates are observed when marsupialization is performed by less experienced practitioners[10,11]. Given the potential benefits of Word catheter placement, there is growing interest in exploring use of it as an alternative treatment. Additionally, the Word catheter is less invasive with less pain and can be performed quicker than the marsupialization. The recurrence rate comparison between the Word catheter versus marsupialization is also still debating. However, Word catheters are not readily available in Thailand and are costly to import. To address this limitation, we have adapted the use of a Foley catheter as a drainage device, referring to this technique as the "modified Word catheter" approach. This study aimed to compare the efficacy of the modified Word catheter with marsupialization in the outpatient management of Bartholin cysts or abscesses, with the primary outcome of recurrence rates, procedural time, and patient outcomes.

Materials and Methods

This study was a single-center, open-label, randomized controlled trial (RCT) conducted at Vachira Phuket Hospital in Thailand. The study protocol was approved by the Institutional Review Board of the Vachira Phuket Hospital Research Ethics Committee (VPH REC 006/2023) and registered in the Thai Clinical Trials Registry (TCTR20230608002). Prior to study initiation, all participating practitioners reviewed standardized instructions for performing both the modified Word catheter placement and the marsupialization procedure.

Women were eligible for inclusion in the trial if they presented with a symptomatic Bartholin gland cyst or abscess with fluctuation. A cyst or abscess was considered symptomatic if the patient reported pain or discomfort due to swelling, with or without signs of inflammation, at the 4 or 8 o'clock position of the vulvar vestibule. The diagnosis was confirmed by a gynecologist. Women were excluded if they had contraindications to either procedure (e.g., comorbidities precluding the safe use of local anesthesia), were unable to understand Thai or English, were under 18 years of age, or declined to

participate.

Eligible women were counseled by their physician or by a dedicated research nurse in the outpatient care unit. After written informed consent had been obtained, a web-based program using a 3x2 random block design with variable block size randomly allocated the women to either a modified Word catheter or marsupialization treatment. Due to the nature of the interventions, it was not possible to mask participants or physicians.

Both interventions were performed immediately in the outpatient unit (procedure room).

Modified Word Catheter (Fig. 1)

The Word catheter is a 5.5 cm long, 15-French silicone device featuring a 3 cm balloon.

For the modified Word catheter, we utilized a No. 14 Foley catheter. Preparation involved trimming the tip of the Foley catheter distal to the balloon prior to use.

The procedure was performed under local anesthesia by a gynecologist (SW) or a resident (CS). A small incision was made over the cyst, followed by the placement of the catheter. The balloon was inflated with 10 mL of sterile water, and the catheter was then tied at 5–6 cm above the balloon and trimmed accordingly. The catheter remained in situ until the follow-up appointment after four weeks or until it fell out. In the latter case, the treating physician provided further management guidance to the patient.

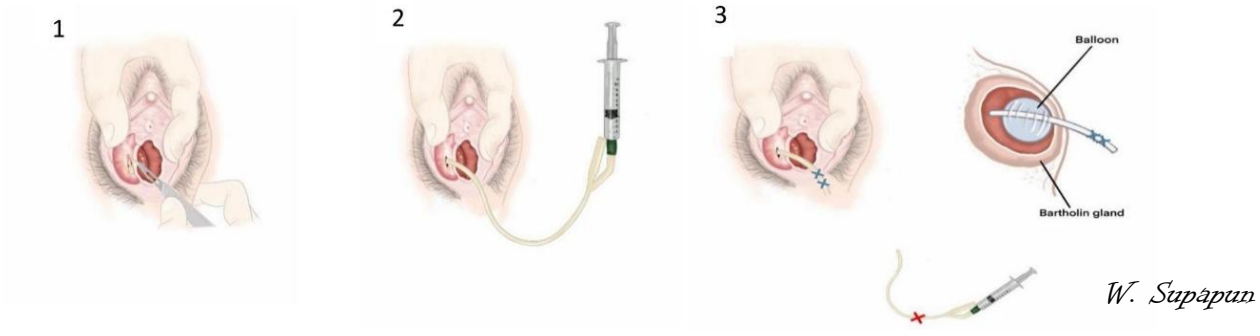

Fig. 1. Illustration of Modified Word catheter procedure.

Marsupialization[3] (Fig. 2)

The marsupialization procedure was performed under local anesthesia by a gynecologist (SW) or a resident (CS). A 1.5 – 3 cm. incision was made over the cyst, after which the cyst wall was everted and approximated to the edge of the vestibular mucosa with interrupted sutures. After 4 weeks, a routine check-up was scheduled.

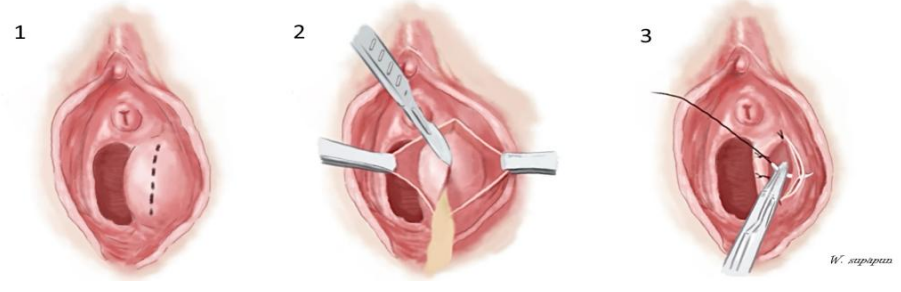

Fig. 2. Illustration of marsupialization procedure.

After obtaining informed consent, participants were interviewed and baseline data were recorded, including age, weight, height, underlying medical conditions, size and location of the Bartholin gland mass, and history of previous Bartholin gland cysts or abscesses. Following treatment and prior to hospital discharge, pain scores during the procedure were assessed and documented. Procedural details, such as the size and location of the mass and the procedural time, were also recorded using a standardized case record form.

One week after treatment, participants were scheduled for an outpatient follow-up visit. During this visit, pain scores on days 1, 2, 3, and 7 post-treatment were recorded, along with the type and quantity of analgesics used. At four weeks post-treatment, wound healing was assessed during a further follow-up visit. At six months, participants were followed-up either in person or by telephone to assess for recurrence. A final follow-up was conducted via telephone at 12 months to evaluate any recurrence of the Bartholin gland cyst or abscess.

The primary outcome was the recurrence of a symptomatic Bartholin gland cyst or abscess requiring treatment within one year of follow-up on the ipsilateral side, confirmed as a clinical diagnosis by a gynecologist (SW). Secondary outcomes included operative time as recorded in the operative notes, pain score during procedure, and peri-operative pain scores assessed at 24 hours, 3 days, and 1 week after treatment. Pain was measured using standardized pain questionnaires.

Based on the results from the WoMan trial conducted by Kroese et al[9], which was an randomized controlled trial, no significant difference was observed in recurrence rates between the Word catheter and marsupialization treatments. Given that the intervention used in the present study follows a similar therapeutic principle to the Word catheter, the researchers adopted a different statistically significant outcome from the WoMan trial—post-treatment analgesic use—as the reference for calculating the sample size.

According to the WoMan trial, the rate of post-treatment analgesic use was 33% in the Word catheter group and 74% in the marsupialization group. We needed to randomize 25 women (two groups of 80% power; two-sided test, alpha error 5%, beta error 20%, and 10% dropout rate).

Statistical analysis was conducted based on the intention-to-treat principle. Differences in dichotomous outcomes were analyzed using the chi-square test or Fisher's exact test when expected frequencies fell below five. Continuous variables were tested for normal distribution. In the case of normal distribution, we compared means of the variables using a t-test, while non-normally distributed variables were analyzed using the Mann–Whitney U test for univariate comparisons. Primary and secondary outcomes were compared by calculating relative risks (RRs) or mean differences, along with their 95% confidence intervals (CIs). Kaplan–Meier survival curves were used to illustrate the time to recurrence of a cyst or abscess requiring surgery within one year of follow-up, and differences between groups were assessed using the log-rank test.

Women lost to follow-up were excluded from the primary analysis. A sensitivity analysis was performed to assess the potential impact of missing data on study conclusions. All statistical analyses were conducted using SPSS, version 22.0. A p value of < 0.05 was considered statistically significant.

Results

Between June 2023 and March 2024, 50 women gave informed consent for randomization and were allocated to either treatment by modified Word catheter (n = 25) or marsupialization (n = 25). One patient in the marsupialization group was lost to follow-up. Therefore, we analyzed the data of 25 women randomized for modified Word catheter and 24 women randomized for marsupialization (Fig. 3).

Baseline characteristics of the two groups were comparable as shown in Table 1. The number of women with a previous ipsilateral cyst or

abscess of Bartholin was 4 (16%) in the modified Word catheter group compared to 8 (33%) in the marsupialization group. Before treatment, the mean pain score was 7.64/10 in women allocated to a modified Word catheter and 7.58/10 in women allocated to marsupialization.

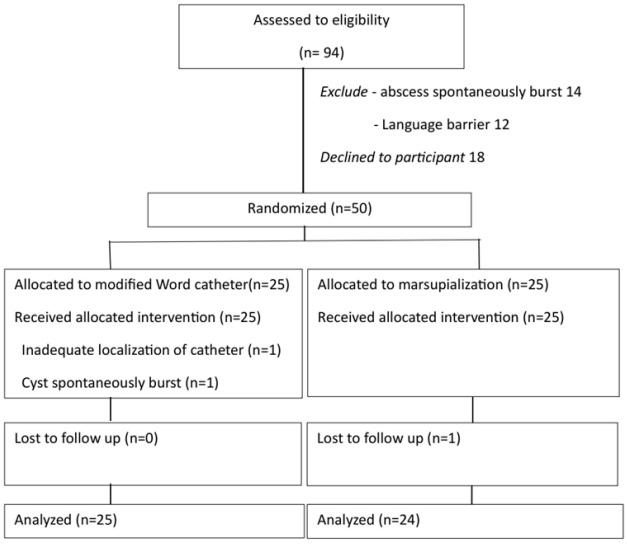

Fig. 3. Flow chart of participants recruitment.

Table 1. Baseline characteristics of women allocated to modified Word catheter or marsupialization for treatment of Bartholin gland cyst or abscess.

	Modified Word catheter (n = 25)	Marsupialization (n = 25)	p value
Age (years), mean (SD)	38.75 (11.53)	35.88 (11.96)	0.397
BMI (kg/m^2), mean (SD)	24.13 (5.14)	22.98 (3.40)	0.406
Underlying, n (%)			0.747
No	18 (72.0)	19 (76.0)	
Yes	7 (28.0)	6 (24.0)	
Hypertension	6 (24.0)	1 (4.0)	0.098
SLE	0 (0.0)	1 (4.0)	0.312
Dyslipidemia	2 (8.0)	2 (8.0)	1.000
Other	2 (8.0)	3 (12.0)	0.637
Smoking, n (%)			0.508
No	18 (72.0)	20 (80.0)	0.508
Yes	7 (28.0)	5 (20.0)	
History of cyst/abscess of Bartholin gland, n (%)			0.185
No	21 (84.0)	17 (68.0)	
Yes, ipsilateral	4 (16.0)	8 (32.0)	
Pain score before treatment (0-10), mean (SD)	7.64 (1.96)	7.60 (1.89)	0.976

BMI: body mass index, n (%): number and percentage, SD: standard deviation, SLE: systemic lupus erythematosus

Of the 25 women randomized to the modified Word catheter group, 23 underwent catheter placement. In one case, placement was unsuccessful, and in another, the abscess ruptured spontaneously

prior to the procedure. Both of these patients were subsequently converted to a marsupialization procedure. In two women, the catheter was removed within the first week due to discomfort. The catheter dislodged spontaneously in two women between 2–7 days, in one woman after 2 weeks, and in two women between 3-4 weeks. At the 4-week follow-up, 16 women (64%) still had the catheter in situ.

All 25 women randomized to the marsupialization group underwent the procedure. One participant was lost to follow-up one week after treatment. Her data were included in the analysis of baseline characteristics, pre-procedural pain scores, procedural time, and perioperative pain scores, but were excluded from the recurrence analysis.

Out of the 50 randomized women, none were lost to follow-up in the modified Word catheter group compared to one in the marsupialization group. The recurrence of the cyst or abscess requiring treatment within one year of follow-up occurred in 3 (12.0%) women in the modified Word catheter group and 3 (12.5%) women in the marsupialization group (RR 0.96; 95% CI 0.21, 4.30; p = 0.957) (Table 2). The median time for recurrence of the cyst or abscess requiring treatment was 6 months after the modified Word catheter and 5 months after marsupialization (p = 0.513). The Kaplan-Meier curve for the time to recurrence of the cyst or abscess needing treatment is shown in Fig. 4. (log-rank test, p = 0.839)

Table 2. Outcomes of women allocated to modified Word catheter or marsupialization for treatment of Bartholin gland cyst or abscess.

Outcomes	Modified Word catheter	Marsupialization	Relative risk or mean difference (95% CI)	p value
Primary outcomes	(n=25)	(n=24)		
Recurrence of the cyst or abscess needing surgery within 1 year	3 (12.0%)	3 (12.5%)	0.96* (0.21 to 4.30)	0.957
Median time to recurrence (months)	6.0	5.0	-	0.513
Secondary outcomes	(n=25)	(n=25)		
Procedure time, median (IQR)	10 (8-12)	15 (14-16)	-	< 0.001
Average pain during treatment, mean (SD)	4.7 (1.8)	6.7 (1.9)	-2.0 (-3.0 to -1.0)	< 0.001
Pain after treatment, mean (SD)				
1 day after treatment	3.8 (1.2)	4.8 (1.5)	- 1.0 (-1.7 to -0.2)	0.024
2 days after treatment	3.6 (1.0)	3.9 (1.4)	- 0.3 (-0.9 to 0.5)	0.624
3 days after treatment	2.3 (0.8)	2.9 (1.6)	- 0.6 (-1.3 to 0.1)	0.074
1 week after treatment	1.1 (1.0)	0.7 (1.0)	0.4 (-0.2 to 0.9)	0.160

* Relative risk
IQR: interquartile range, SD: standard deviation

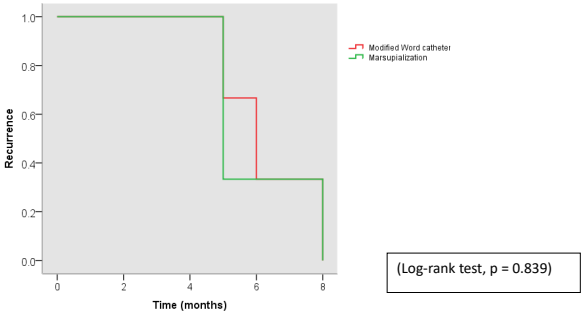

Fig. 4. Kaplan-Meier curves for time to recurrence of the Bartholin cyst or abscess after treatment.

Women who underwent the modified Word catheter procedure had a procedural time ranging 8 to 12 minutes, with a median time of 10 minutes. In comparison, the marsupialization group had procedural times ranging from 14 to 16 minutes with a median time of 14.5 minutes ($p < 0.001$).

Pain questionnaires were returned by all 50 women who participated in the study. Supporting information displays perioperative pain scores, measured on a 10-points scale, for women allocated to each group. The average pain experienced during the placement of the modified Word catheter was 4.7 out of 10, compared to 6.6 out of 10 for marsupialization ($p = 0.001$). Mean pain scores in the days following treatment can be found in Table 2. One week after treatment, the mean pain scores for the modified Word catheter and marsupialization groups were 1.1 out of 10 and 0.7 out of 10, respectively ($p = 0.179$).

In a sensitivity analysis, the assumption that one woman lost follow-up in the marsupialization group had a recurrence event did not affect our results (data not shown).

Discussion

Marsupialization is still the standard treatment for Bartholin cysts or abscesses in Thailand. In our study, the recurrence rate after marsupialization was 12.5%, which was consistent with the range reported in the literature (0 –13%)[1, 2, 4-8], although it may be considered relatively high. When analyzing factors related to recurrence, we discovered that the type of anesthesia administered during the procedure could impact the results. Specifically, local anesthesia was linked to a higher recurrence rate, while general or spinal anesthesia seemed to decrease the chances of recurrence[7, 8].

In previous studies, recurrence rates with catheter drainage using the commercial Word catheter have been reported to range from 2.7% to 17.4%[1, 2, 4-8]. In our study, we utilized a modified approach by using a Foley catheter, which is functionally equivalent to the Word catheter, for drainage. The recurrence rate observed in the modified Word catheter group (12%) was similar to the rates reported for the standard Word catheter.

At the one-year follow-up, the recurrence rates were 12% in the modified Word catheter group and 12.5% in the marsupialization group. These results closely resembled those of the WoMAN trial[9], which reported one-year recurrence rates of 12% for the standard Word catheter and 10% for marsupialization. To our knowledge, our study is the first RCT to directly compare the modified Word catheter with marsupialization. Given the similar recurrence outcomes, we concluded that the modified Word catheter demonstrated comparable efficacy to the standard Word catheter in the management of Bartholin cysts or abscesses.

Regarding other outcomes, the median procedural duration was 4.5 minutes shorter for the modified Word catheter compared to marsupialization. This suggested that the modified Word catheter was easier to handle. Similar findings have been reported in several studies comparing the procedural difficulty scores between Word catheterization and marsupialization[12-15].

In addition to its ease of application, our study found that the average pain experienced during treatment was lower in the modified Word catheter group compared to the marsupialization group. This finding contrasted with the WoMan trial[9], which reported higher mean pain scores during treatment in the Word catheter group compared to the marsupialization group (4.9/10 vs 1.9/10, respectively; $p < 0.001$). The discrepancy may be attributed to differences in analgesic methods: in our study, local anesthesia was used for both groups, whereas in the WoMan trial, local anesthesia was administered for the catheter group and general or spinal anesthesia for the marsupialization group.

In the context of managing Bartholin's cyst or abscess on an outpatient basis, we believe that using local anesthesia is preferable. Our findings suggested that using the modified Word catheter results in greater patient tolerance of pain in these situations.

There were some limitations in this study. First,

this study was conducted as an open-labelled RCT as these procedures were unable to perform blindly. Second, subjective evaluation was evaluated and should be interpreted cautiously. Finally, sample size was quite small. Even though it met with the sample size calculation, this calculation was performed based on analgesic use, not the recurrent rate. Further larger RCTs may be needed to confirm the results of this study.

Conclusion

Both modified Word catheter placement and marsupialization yielded comparable 1-year recurrence rates for the treatment of symptomatic Bartholin gland cysts or abscesses. However, the modified Word catheter offered advantages in terms of patient tolerance, faster symptom relief, and lower procedural costs, supporting its use as the preferred first-line outpatient intervention.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Peripheral Blood Natural Killer Cells and Th1 Cytokines in Unexplained Female Infertility

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ABSTRACT

Objectives: To compare the percentage and absolute numbers of peripheral blood (PB) natural killer (NK) cells and its subsets and levels of T helper cells 1 (TH1) cytokines [interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα)] in women with unexplained infertility with that of healthy fertile women.

Materials and Methods: This was a three-year study which included 31 women with history of UI and 33 fertile controls. Flow cytometry was done on ethylene di-amine tetra-acetic acid samples to determine the percentage and absolute count of total PB NK cells and its subsets. Enzyme linked immunosorbent assay was done on serum samples for IFNγ and TNFα.

Results: The ratio of mean percentages of CD56dim and CD56bright NK cells [31.36 in patients vs 18.06 in controls (p = 0.034)], mean percentage of CD56+CD16+ NK cells [7.04 in patients vs 4.96 in controls (p = 0.034)] and CD56dim CD16+NK cells [81.02 in patients vs 60.49 in controls (p = 0.004)] was significantly increased in infertile women compared to fertile women. The percentage and absolute count of CD56+CD16- NK cells [p = 0.017 and p = 0.022, respectively] and CD56dimCD16- NK cells [p = 0.002 and p = 0.02, respectively] was significantly raised in fertile controls compared to infertile patients. Mean percentage of total PB NK cells, mean percentage and absolute count of CD56bright, CD56dim, CD56brightCD16+, CD56brightCD16-NK cells and mean serum levels of TNF-α and IFN-γ in infertile groups were higher but not significant compared to fertile group.

Conclusion: CD56+CD16+ NK cells which constitute the major population of PB NK cells and its major subset, CD56dim CD16+ NK cells was significantly raised in unexplained infertile women.

Keywords: Natural killer cells, TNF-α and IFN-γ, unexplained infertility.

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Introduction

Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse"[1]. The combined pooled global prevalence of infertility according to a study is around 10%[2]. There are various causes of female infertility out of which unexplained infertility, which is a diagnosis of exclusion, accounts for around 25% of patients investigated for reproductive failure after tests of semen analysis, concentrations of progesterone in mid-luteal phase, tubal patency and uterine cavity are normal[3]. Natural Killer (NK) cells are the first line cellular defense mechanism and are in close contact with conceptus and placenta. NK cells are part of innate immune system and express the cell surface antigens CD16 and CD56. On the basis of intensity of CD56 expression, NK cells are divided into two subsets: CD56dim and CD56bright. NK cells that are cytotoxic in vitro are CD56dim. However, little cytotoxic activity is caused by CD56bright NK cells, but they produce immunoregulatory cytokines like interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα)[4].

Increased number of uterine NK (uNK) cells are present in mid-secretory phase of the menstrual cycle although the underlying mechanism is not known. There are two theories given for this: peripheral blood natural killer (PB NK) cells are recruited which differentiate into uNK cells in uterine microenvironment by various organized processes or they are derived from proliferation and differentiation of stem cells in utero or the endogenous NK cell population present in endometrium[5, 6]. Fetal non-polymorphic human leucocyte antigen (HLA-G) and HLA-E are recognized by uterine NK cells which results in the secretion of T- helper type 2 (Th2) cytokines leading to a successful pregnancy outcome[7-10].

PB NK cells are mainly (90%) CD56dim CD16+ and a minor population (10%) of PB NK cells are CD56bright CD16-[11]. Evidence suggests that increased proportion and activity of PB NK cells determined by immunophenotyping are related to recurrent spontaneous abortion (RSA), so functional assays for NK cells cytotoxicity are being used to monitor treatment and pregnancy outcomes[12, 13]. IV immunoglobulins (IVIg) or allogenic lymphocyte treatment results in successful pregnancy in RSA by decreasing the percentage and activity of NK cells[14, 15]. These treatments also result in production of Th2 cytokines (IL-4, IL-10) which subsequently decrease Th1/Th2 ratio and thus favour a successful pregnancy outcome[16]. Th1 cells produce TNFα, IFNγ and IL-2. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13[17, 18]. It has been proposed that successful pregnancy results in an immune bias towards T helper type 2 (Th2) immunity[19]. As both unexplained infertility and RSA are immune related conditions, so in this study, we have tried to determine and compare the levels of peripheral blood NK cells, its subsets and serum levels of Th1 cytokines (TNFα and IFNγ) in women with unexplained infertility and in healthy fertile women.

Materials and Methods

This was a three-year study which included 31 women with unexplained infertility with regular, ovulatory cycles, at least one patent fallopian tube and < or = 40 years of age. Exclusion criteria included women with known uterine fibroids, structural abnormalities of uterus, history of pelvic inflammatory disease (PID), anovulatory cycles polycystic ovarian syndrome (PCOS), immunologic abnormalities, history of diabetes mellitus (DM), thyroid disease or any chronic disease, infectious and inflammatory diseases or partner with male factor infertility. Thirty-three healthy fertile women volunteers matched for age, body mass index (BMI), ethnicity to cases who were < or = 40 years of age, non-pregnant, having > or = 1 healthy child with no history of pregnancy loss or infertility, immunologic abnormalities like systemic lupus erythematosus (SLE), anti-phospholipid antibody (APLA) etc, history of DM, thyroid disease or any chronic disease, infectious and inflammatory diseases, no history of PID were included in the study.

Informed consent was taken. Blood samples

were taken in two vials, one ethylene di-amine tetra-acetic acid (EDTA) and one plain vial during the follicular phase (day 10-14) of the menstrual cycle from all infertiles and fertiles during their routine sampling for other investigations.

Flow cytometric immunophenotyping of blood samples was performed using five colour flow cytometer (Beckman Coulter FC500 Flow Cytometer). Samples were processed using stain-lyse-wash technique. A four colour analysis was performed using antibody bound to following flurochromes, fluorescein isothiocynate (FITC), Phycoerythrin (R Phycoerythrin), Phycoerythrin-Cyanine 5 (R Phycoerythrin-Cyanin 5.1), R Phycoerythrin-Texas Red-X. Antibodies included were provided by Beckman Coulter and included a cocktail of CD16FITC, CD56PE, CD3ECD and CD45PC5. Flow cytometric data was acquired using CoaXPress acquisition software. Each tube was run on instrument as per panel and events were acquired in the form of dot plots. Maximum number of possible events (upto 1 lakh) was acquired. Gating was done using forward scatter (FSC) vs side scatter (SSC), CD45 vs SSC, CD56 vs CD3, CD56 vs. CD16. The data was stored in list mode files and was analysed using CXP analysis software for total percentage and absolute numbers of total NK cells and its various subsets.

The enzyme-linked immunosorbent assay (ELISA) was also done on the serum samples of the same patients for TNF alpha and IFN gamma using Diaclone kit made in France with a sensitivity of 8 pg/ml.

Ethical clearance was obtained from Ethics Committee for Human Research, Lady Hardinge Medical College, New Delhi.

Results

The various demographic and clinical parameters are listed in Table 1. According to the percentage of total NK cells (CD56+CD3-), the infertiles and fertiles were divided into 3 groups comprising of < 5 % NK cells, 5-12% NK cells and > 12% NK cells as shown in Table 2. These results showed that most of the infertiles and fertiles had NK cells in the range of 5-12% and only 6 infertile women and 6 fertile controls showed NK cells > 12%. The mean value of total PB NK cells and their various subsets is given in Table 3. These results showed that the percentage of CD56+CD16+, CD56dim CD16+ PB NK cells was significantly raised in infertile women compared to fertile controls whereas the percentage and absolute count of CD56+CD16- and CD56dimCD16- was significantly raised in fertile controls compared to infertile patients. The rest of the subsets did not show any significant difference between the two groups. The mean serum levels of TNF-α and IFN-γ in infertile group were higher but did not show any significant difference compared to the controls as shown in Table 4. Fig. 1 shows flow cytometric findings of an infertile patient. Fig. 2 shows flow cytometric findings of fertile control.

Table 1. Demographic and clinical parameters of patients and controls.

Parameters	Patients	Controls
Number	31	33
Age (mean in yrs.)	27.03	29.64
Type of infertility	20-primary	-
	11-secondary	
Number of live births (range)	0-1	1-4
Any history of abortion	10/31	1/33
History of tubal ectopic pregnancy	3/31	0

Table 2. Distribution of total natural killer cells in patients and controls.

		Group		Total	Chi-square	p value
		Patients	Control			
Total NK cells % (CD56+CD3-)	0-5%	6	9	15		
	5-12%	19	18	37		
	> 12%	6	6	12		
Total		31	33	64	0.565	0.754

NK: natural killer

Table 3. Mean value of total peripheral blood natural killer cells and its various subsets in patients and controls.

Parameter	Patients (mean) (percentage / absolute value)	Controls (mean) (percentage / absolute value)	p value (percentage / absolute value)
Total NK cells (CD56+CD3-)	8.12 / 139.71	7.70 / 153.85	0.684 / 0.587
CD56 bright CD3- NK cells	0.58/11.71	0.44/8.42	0.512/0.557
CD56 dim CD3- NK cells	7.54/128.03	7.26/146.64	0.779/0.455
Ratio of CD56dim NK cells/ CD56bright NK cells	31.36	18.06	0.034
CD56+CD16+	7.04 / 120	4.96 / 96.15	0.034 / 0.288
CD56dimCD16+ (out of total NK cells)	81.02 / 111.97	60.49 / 92.33	0.004 / 0.369
CD56brightCD16+ (out of total NK cells)	4.47 / 8.10	2.82 / 3.76	0.242 / 0.35
CD56+CD16-	1.08 / 19.65	2.74 / 58.91	0.017 / 0.022
CD56dim CD16-(out of total NK cells)	11.31 / 15.91	31.86 / 54.24	0.002 / 0.02
CD56brightCD16- (out of total NK cells)	2.69 / 3.74	4.60 / 4.67	0.089 / 0.466

PB: peripheral blood, NK: natural killer, CD: cluster of differentiation.

Table 4. Comparison of serum IFN-γ AND TNF-α levels (pg/ml) between patients and controls.

	TNF-α		IFN-γ	
	Patients	Controls	Patients	Controls
N	31	33	31	33
Mean	40.49	19.72	5.89	3.39
Median	16.5	10.3	1.37	2.06
Std. Deviation	62.56	37.29	11.53	5.96
p-value	0.109		0.275	

IFN-γ: interferon-gamma, TNF-α: tumor necrosis factor-alpha

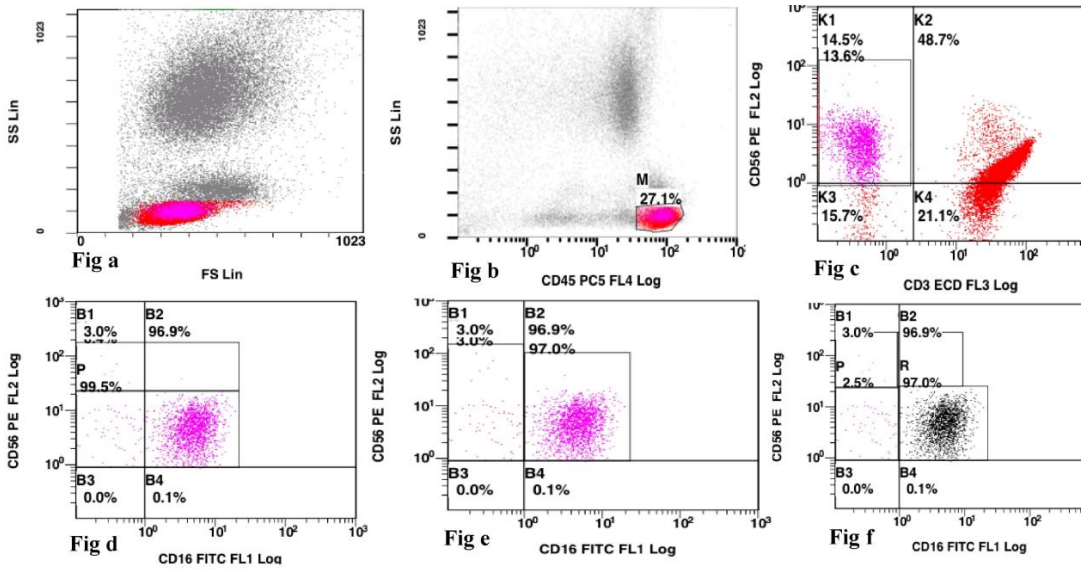

Fig. 1. Flow cytometric findings of an infertile woman a) Side scatter vs CD45 showing the percentage of gated lymphocytes out of total leucocytes = 27.1%. b): CD56 vs CD3 showing total NK cells which are CD56+CD3-:13.6%(pink). c): CD56 vs CD16 show that out of total NK cells, 99.9% are CD56+CD16+ NK cells and 0.1% are CD56+CD16- NK cells. d-e): CD56 vs CD16 showing percentages of various subtypes of NK cells out of total NK cells: CD56brightCD16+ NK cells: 97% and CD56dimCD16+ NK cells: 3%, CD56brightCD16- NK cells: 2.5%, CD56dimCD16- NK cells: 0%.

CD: cluster of differentiation, NK: natural killer.

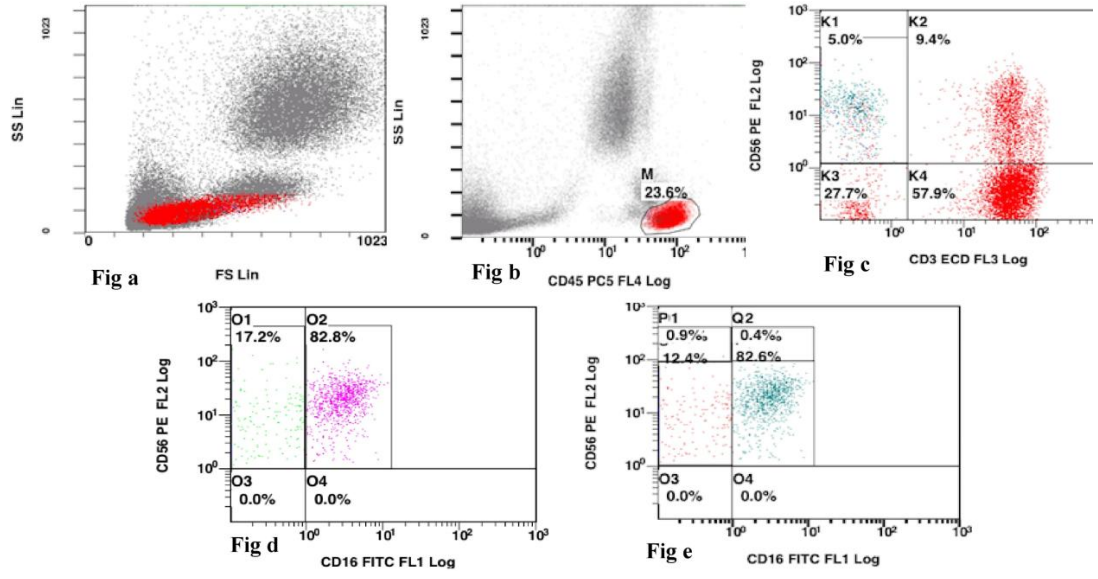

Fig. 2. Flow cytometric findings of a fertile control a): SSC vs CD45: Showing gated lymphocytes =23.6%. b):CD56 vs CD3 showing total CD56+CD3- NK cells (pink) out of total lymphocytes:5%. C-d): CD56 vs CD16 showing percentage of all the subtypes of NK cells out of total NK cells; CD56+CD16- NK cells:82.8%, CD56+CD16+ NK cells: 17.2%, CD56brightCD16+NK cells: 0.4%, CD56dimCD16+ NK cells: 82.6%CD56brightCD16- NK cells: 0.9%, CD56dimCD16- NK cells: 12.4%.

SSC: side scatter, CD: cluster of differentiation, NK: natural killer.

Discussion

Infertility is an increasing medical and social issue. Immune system plays a definite role in implantation process of the embryo. Since many years, unexplained infertility has been suspected to have an immunological basis[20]. A study by Park et al[21] reported that the levels of peripheral NK (pNK) cells mirror those of decidual NK (dNK) cells, suggesting that pNK cell measurement may serve as a clinically valuable marker for predicting pregnancy outcomes. Although some other studies have refuted this claim[22, 23].

Many studies have tried to find out the relationship between altered PB NK cell parameters and RPL[12, 13]. It is speculated that an elevation of natural killer (NK) cells may have an effect on reproductive performance, and PB NK cell levels are currently being used as a diagnostic test to guide the initiation of therapies in patients with infertility. However, not much research has been done regarding the various NK cell parameters in women with UI. So, in this study we have tried to evaluate the percentage and absolute count of NK cells and its subsets along with levels of Th1 cytokines to determine their diagnostic utility and as a therapeutic target in women with unexplained infertility and compared them with that of healthy fertile women.

It has earlier been reported that the normal percentage of total NK (CD56+CD3-) cells in peripheral blood is around 5-12% and >12% was taken as elevated NK cell percentage [24], so the infertiles and fertiles were divided into 3 groups: - < 5 % NK cells, 5-12% NK cells and >12% NK cells. Most of the infertiles and fertiles had normal range (5-12%) of NK cells and only 6 infertile women and 6 controls show NK cells >12%. So, no single cut off value could be established as normal NK cell count.

A few previous studies[25] have reported the percentage of total PB NK cells (CD56+) to be significantly higher in infertile subjects with multiple IVF failures compared to fertile controls. However, in the present study, the percentage and the absolute count of total PB NK cells did not show a significant difference between the two groups.

Two clearly different subgroups of human NK cells are identified by cell surface expression of CD56 (D56bright or CD56dim). Although both PB NKcells and uterine NK (uNK) cells show the surface CD56, however PB NK cells differ from uNK cells in both phenotypically and functionally with the fact that almost 10% of pNK cells are similar to uNK cells[26]. There are two main subsets of PB NK cells: the majority (more than 90%) which lyses target cells express CD56 at low density and CD16, and referred to as CD56dim CD16+ cells; while approximately 10% of PB NK cells have high surface expression of CD56, but do not express CD16, and are referred to as CD56bright CD16– cells. These PB NK cells have little or no cytotoxic activity but produce abundant cytokines. The relationship between these two main subsets of PB NK cells is not very clear; and they may play completely different roles in the human immune response[27].

Our study showed a significant increase in the mean ratio of the percentage of CD56dim and CD56 bright cells in infertiles than in fertiles. Only a few previous studies have calculated this ratio, which was higher but not significant[25]. Our study did not show any significant difference in the percentage of CD56dim cells similar to the findings reported by McGrath et al[28].

The mean percentage of CD56+ CD16+ NK cells was significantly raised in women with UI compared to fertile controls. The mean absolute count was also raised in women with unexplained infertility compared to fertile controls, however it did not reach statistically significant levels. This is in concordance with the finding of Fukui et al[29] who reported that on the day of embryo transfer in IVF patients, the percentage of these cells was significantly higher ($p < 0.05$) in the failed group than in the implanted group.

Mardanian et al[30] reported that women with failed IVF had significantly higher levels ($p < 0.0001$) of CD56dim CD16+ NK cells compared to fertile women. The mean percentage of peripheral blood

CD56dim CD16+ NK cells out of total NK cells was significantly raised in infertile group compared to the fertile group between the two groups. The mean percentage and absolute count of CD56bright CD16+ NK cells which constitutes a minor subset of CD56+CD16+ NK cells did not show any significant difference.

This shows that although the total CD56+(dim + bright) CD16+ NK cells and its major subpopulation, CD56dim CD16+ NK cells were significantly increased in infertile women, CD56bright CD16+ which constitutes a minor subset, did not show any difference between the two groups. There are no published studies to have reported the levels of this particular subset (CD56bright CD16+) in peripheral blood comparing infertile and fertile women.

The mean percentage and absolute count of peripheral blood CD56+CD16- NK cells showed a significant increase in fertile control group compared to infertile women. Similar results were seen in the study done by Michou et al[31].

The mean percentage and absolute counts of CD56bright CD16-, constituting the major population of NK cells in endometrium (uterine NK cells) but a minor subset of total NK cells in peripheral blood were increased in fertile controls compared to infertile women, they did not reach statistically significant levels. This finding is important as these cells are known to take part in successful implantation of the embryo and increase in normal pregnancy. So, these cells being more in fertiles in PB also supports this evidence. Mardanian et al [30] reported no significant differences in these cells in women with failed IVF and with successful IVF.

The mean percentage and absolute counts of CD56dim CD16- NK cells, which constitutes a minor subset of CD56+ CD16- NK cells, showed a significant increase in fertile controls compared to infertile women.

To the best of our knowledge, no study till date has reported the levels of this particular subset (CD56dim CD16-) in peripheral blood comparing infertile and fertile women. So, this subset of NK cells could prove to be a useful marker in infertile women, however more studies with larger sample size are required to prove this finding.

Normal pregnancy has been associated with a shift from Th-1 type and a bias towards Th-2 response[32]. The mean serum levels of TNF-α in infertile group were higher than the fertile group but were not statistically significant ($p = 0.109$). Few previous studies[33] have reported a significant increase in infertile women and with failed IVF treatment respectively compared to controls. These studies corroborated with our finding of raised serum levels of TNF-α in infertile group compared to the fertile group but our results did not reach statistically significant levels which may be because of smaller sample size. Studies done by Okpalaji et al[20] reported that mean serum TNF-α levels in infertile women were not significantly different ($p = 0.26$ and $p = 0.902$ respectively) from fertile women.

The mean serum levels of IFN-γ in infertile group was higher than in control group was but was statistically not significant ($p = 0.275$). Previous study by Thum et al[34] reported a similar finding in women after IVF, although the levels were raised but showed no statistically significant difference between non-pregnant and pregnant group and between miscarriage and live birth group which is in concordance with our study. Okpalaji et al[20] reported that infertile women had significantly raised levels of serum TNF-α compared to fertile controls.

Thus, it is shown in our study that CD56+CD16+ NK cells which constitute the major population of PB NK cells and its major subset, CD56dim CD16+ NK cells was significantly raised in unexplained infertile women as shown in many previous studies. CD56+CD16- NK cells which is a minor population of PB NK cells was significantly raised in fertile women compared to women with unexplained infertility. However, its major subset, CD56bright CD16- was also raised in fertile controls but it did not reach statistically significant levels. Although most previous studies[25] report that total PB NK cells was significantly higher in infertile women compared to

fertile controls, in our study the percentage of total peripheral blood NK cells in infertile group was higher but statistically not significant compared to fertile controls. According to a previous study[24], the normal percentage of NK cells in PB is 5-12% and > 12% is taken as elevated NK cell percentage. However, in our study, most of the infertiles and fertiles had NK cells in the range of 5-12% and only 6 infertile women and 9 controls showed NK cells >12%. The mean serum levels of TNF-α and IFN-γ in infertile group were higher but statistically not significant compared to fertile group.

Conclusion

This study can provide an insight into the pathophysiology of unexplained infertility which shows significantly altered NK cell parameters which can be treated using various therapies like IVIg and steroids. This is the first study that has calculated all the major subsets of PB NK cells using flow cytometry in UI and fertile women. However, the major limitation of this study was the small sample size and overlapping values of total NK cells and its subsets, serum levels of TNF-α in infertiles and fertiles. So, further large-scale studies are required to confirm our findings.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence of Illicit Drug use during Pregnancy between Teenage and Non-teenage in Thailand

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ABSTRACT

Objectives: The primary outcome was to compare the prevalence of illicit drug use during pregnancy between teenage and non-teenage. The secondary outcomes were to investigate the possible factors predicting of illicit drug use before and during pregnancy and also to compare the incidence of adverse maternal/neonatal outcomes and overall adverse pregnancy outcomes between the participants who had a history of illicit drug use during pregnancy and those who did not.

Materials and Methods: This prospective cross-sectional study was conducted at HRH Princess Maha Chakri Sirindhorn Medical center, Srinakharinwirot University, Thailand, between September 2024 and May 2025. The participants were asked to complete a questionnaire to provide their information.

Results: 310 participants were enrolled. The prevalence of participants who had a history of any illicit drug use before pregnancy was 50/62 (80.6%) and 170/248 (68.5%) in the teenage and non-teenage group, respectively. Teenage pregnancy was not actually found to be a factor that predicted the risk of illicit drug use during pregnancy (adjusted odds ratio 0.716, 95%CI 0.305, 1.682, p = 0.443), while a lower educational level (junior high school or lower), more than 7-hour social media use per day, and age at first sexual intercourse were statistically significantly associated with illicit drug use. Adverse neonatal outcomes were significantly higher in the participants who had a history of illicit drug use during pregnancy than those who did not.

Conclusion: Prevalence of illicit drug use during pregnancy in teenage was not different from in non-teenage. Teenagers alone were not at risk of engaging in illicit drug use. A level of education of junior high school or lower, more than 7 hours per day social media use, and a young age at first sexual intercourse were significant factors associated with a higher prevalence of illicit drug use during pregnancy.

Keywords: teenage, pregnancy, illicit drug, alcohol, smoking, pregnancy outcome.

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ความชุกการใช้ยาเสพติดผิดกฎหมายระหว่างตั้งครรภ์ระหว่างหญิงตั้งครรภ์วัยรุ่นและไม่ใช่วัยรุ่นประเทศไทย

ชญานิศ ขอประเสริฐ, กิตติพงษ์ คงสมบูรณ์, ธารางรัตน์ หาญประเสริฐพงษ์

บทคัดย่อ

วัตถุประสงค์*: วัตถุประสงค์หลักเพื่อเปรียบเทียบความชุกของการใช้ยาเสพติดผิดกฎหมายระหว่างตั้งครรภ์ระหว่างหญิงตั้งครรภ์วัยรุ่นและไม่ใช่วัยรุ่น วัตถุประสงค์รองเพื่อศึกษาปัจจัยเป็นไปได้ในการคาดคะเนการใช้ยาเสพติดผิดกฎหมายก่อนและระหว่างการตั้งครรภ์ และเปรียบเทียบอุบัติการณ์ของการตั้งครรภ์ไม่พึงประสงค์ต่อมารดา/ทารกในครรภ์และโดยรวมระหว่างหญิงตั้งครรภ์ที่มีประวัติการใช้สารเสพติดผิดกฎหมายระหว่างตั้งครรภ์กับหญิงตั้งครรภ์ที่ไม่ใช้*

วัสดุและวิธีการ*: การศึกษาแบบตัดขวาง ไปข้างหน้า ดำเนินการที่มหาวิทยาลัยศรีนครินทรวิโรฒ ประเทศไทย ระหว่างเดือนกันยายน พ.ศ. 2567 ถึงเดือนพฤษภาคม พ.ศ. 2568 อาสาสมัครได้รับการขอให้กรอกแบบสอบถามเพื่อให้ข้อมูลของตน*

ผลการศึกษา*: อาสาสมัครเข้าร่วมการศึกษา 310 คน ความชุกของผู้เข้าร่วมที่มีประวัติการใช้ยาเสพติดผิดกฎหมายก่อนตั้งครรภ์คือ 50/62 (ร้อยละ 80.6) และ 170/248 (ร้อยละ 68.5) ในกลุ่มวัยรุ่นและไม่ใช่วัยรุ่นตามลำดับ การตั้งครรภ์ในวัยรุ่นไม่เป็นปัจจัยที่ทำนายความเสี่ยงของการใช้ยาเสพติดผิดกฎหมายในระหว่างตั้งครรภ์ ในขณะที่ระดับการศึกษาที่ต่ำกว่า (ระดับมัธยมต้นหรือต่ำกว่า) การใช้โซเชียลมีเดียมากกว่า 7 ชั่วโมงต่อวัน และอายุเมื่อมีเพศสัมพันธ์ครั้งแรก มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการใช้ยาเสพติดผิดกฎหมาย ผลลัพธ์ที่ไม่พึงประสงค์ต่อทารกแรกเกิดสูงกว่าอย่างมีนัยสำคัญในผู้เข้าร่วมที่มีประวัติการใช้ยาเสพติดผิดกฎหมายในระหว่างตั้งครรภ์เมื่อเทียบกับผู้ที่ไม่มีประวัติ*

สรุป*: ความชุกของการใช้ยาเสพติดผิดกฎหมายระหว่างตั้งครรภ์ในกลุ่มวัยรุ่นไม่แตกต่างกับกลุ่มที่ไม่ใช่วัยรุ่น การตั้งครรภ์ในวัยรุ่นไม่เป็นปัจจัยเสี่ยงของการใช้สารเสพติดผิดกฎหมายทั้งก่อนและระหว่างตั้งครรภ์ ระดับการศึกษาในระดับมัธยมต้นหรือต่ำกว่า การใช้โซเชียลมีเดียมากกว่า 7 ชั่วโมงต่อวัน และการมีเพศสัมพันธ์ครั้งแรกตั้งแต่อายุยังน้อย เป็นปัจจัยสำคัญที่เกี่ยวข้องอย่างมีนัยสำคัญกับอัตราการใช้ยาเสพติดผิดกฎหมายที่สูงขึ้นในระหว่างตั้งครรภ์*

คำสำคัญ*: วัยรุ่น, ตั้งครรภ์, ยาเสพติด, แอลกอฮอล์, สูบบุหรี่, ผลการตั้งครรภ์*

Introduction

Substance-use disorder is a medical impairment or condition caused by the use of one or more harmful substances[1], legal or illegal, such as cigarettes, alcohol-containing beverages, marijuana, cocaine, amphetamine and opioids[2-4]. Alcohol-containing beverages are any beverage that contains ethyl alcohol (EA), such as wines made from a variety of fruits, such as grapes, peaches, plums or apricots, where the fruits are crushed and fermented in large vats to produce wine. Moreover, while different types of alcohol-containing beverages will have different levels of EA the EA will still have the same effect on the fetus. Fetal alcohol spectrum disorders (FASDs) can occur when the mother intakes alcohol either periconception or during later pregnancy. FASDs cover a wide range of abnormalities, including fetal alcohol syndrome (dysmorphic facial features, prenatal and/or postnatal growth impairment, abnormal brain growth/morphogenesis/physiology and neurobehavior impairment), partial fetal alcohol syndrome, alcohol-related birth defects (cardiac and renal anomalies, orthopedic problems, abnormalities of the eyes and ears, ventral wall defects), alcohol-related neurodevelopmental disorder, and neurobehavioral disorder associated with prenatal alcohol exposure. No amount of EA is considered safe in pregnancy[5].

Smoking is another harmful behavior, depending on the substance, in which a person inhales substances into the body, mostly gases, which may contain chemical agents, natural essential substances, such as herbs or natural fragrances, and even addictive substances that are harmful to the body[2]. In addition to natural substances, such as lavender[6], which have been reported to be inhaled for pain relief in pregnant women, cigarettes (common forms of tobacco) and marijuana are addictive but harmful substances that are smoked and may be used by some pregnant women. Cigarette smoking has been linked to several adverse pregnancy outcomes, including ectopic pregnancy, placenta previa, abruptio placenta, preterm premature rupture of membranes, low birthweight, intrauterine growth restriction, intrauterine fetal death, neonatal respiratory and gastrointestinal disease, and may necessitate neonatal admission to the intensive care unit (ICU)[2]. Meanwhile, marijuana, which is often combined with tobacco, has both depressant and stimulating effects on the central nervous system (CNS) of pregnant women[3]. CNS stimulant, facial cleft, cardiac anomalies and fetal growth restriction have been reported in infants exposed to amphetamine, and cocaine in utero[4]. Marijuana and cocaine have been associated with developmental delay, preterm birth and low birth weight[7, 8].

A teenager is defined as a young person aged between 13 to 19 years old[9]. They are considered to have a uniquely vulnerable status related to their growth and development stage. Teenagers are exposed to intense physical, emotional and social changes, which make them prone to several potential problems, including mental health disorders, abuse or violence and harmful behaviors, including alcohol and drug use[10]. Although, there has been research into illicit drug use in teenagers, there are few reports about it in regard to pregnancy. Furthermore, there is limited information about illicit drug use in teenagers in Thailand, and, to the best of our knowledge, there has been no reported study on illicit drug use in teenage pregnancy in Thailand. Consequently, we conducted this study. The primary outcome was to compare the prevalence of illicit drug use during pregnancy between teenage and non-teenage. The secondary outcomes were to investigate the possible factors predicting of illicit drug use before and during pregnancy and also to compare the incidence of adverse maternal/neonatal outcomes and overall adverse pregnancy outcomes between the participants who had a history of illicit drug use during pregnancy and those who did not.

Materials and Methods

This prospective cross-sectional study enrolled pregnant women who visited the Obstetric Unit of the Department of Obstetrics and Gynecology, HRH

Princess Maha Chakri Sirindhorn Medical center, Faculty of Medicine, Srinakharinwirot University, Thailand, between September 2024 and May 2025. Pregnant women who could not understand Thai were excluded from the study. The study was approved by the institute's ethics committee (SWUEC-671006) and was registered on the Thai Clinical Trials Registry (TCTR 20230918001). Informed consent was obtained from all the participants. The participants were asked to complete a questionnaire to provide their general information, which included their maternal age, race, education, parity, gravidity, occupation, religion, family income, legal personal status in Thailand, duration of social media using in a day, marriage status, maternal family status (pregnant women's parents' statuses), age at first sexual intercourse, and history of a diagnosis of sexually transmitted diseases (STD). Then, the patient history was taken concerning illicit drug use before and during pregnancy by the 1st (C.K.) or 3rd (T.H.) author of this study and recorded in a private and confidential section. All participants were reassured that all their information was confidential and securely stored and they were asked to be frank and to provide as much true information as possible. In cases of patients' presenting with illicit drug use, which they properly and voluntarily introduced, they were offered the opportunity to be referred to an expert physician for substance abuse treatment, without any formal legal notification.

Following, all the participants routinely received antenatal, intrapartum and postpartum maternal/neonatal care at the Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University. Pregnancy and neonatal outcomes were recorded.

In terms of drug use and the different types, we defined these as follows.

Alcoholic beverages, meaning all beverages that contain EA, regardless of the raw material the EA was made from or the EA concentration in the beverage. Furthermore, alcohol drinkers were classified into different categories based on their drinking patterns. The definition was modified for clarity in clinical data collection[11, 12]:

I. Social drinking: pattern corresponding to consuming alcohol in social settings without reaching the point of being drunk.

II. Binge drinking: pattern corresponding to consuming alcohol to the point of intoxication, regardless of the frequency of drinking.

III. Problem drinking: pattern corresponding to regularly consuming alcohol to the point of intoxication.
IV. Alcoholism: pattern corresponding to consuming alcohol to the point of it causing physical or mental health problems that require medical treatment.

Cigarette smoking or vape use, classified into[13]:

I. Social smoking: pattern corresponding to cigarette smoking in social settings.

II. Less than 3 years smoking (L3): history of regular smoking of more than 10 cigarettes per day for less than 3 years.

III. More than 3 years smoking (M3): history of regular smoking of more than 10 cigarettes per day for more than 3 years.

IV. Vape smoking: history of vape smoking, either with/without cigarette smoking.

V. Junior smoking: history of starting smoking at junior age of less than 18 years old.

In cases whose smoking characteristics could be categorized into multiple groups, the participants were classified into the higher numbered group, e.g., a participant who started cigarette smoking at an age less than 18 years old and who also vaped would be classified into group V (junior smoker).

In terms of illicit drugs, amphetamine users were defined as anyone who had a history of using amphetamine-containing drugs or substances regardless of the form, amount, or dosage. Similarly, marijuana users were defined as anyone who had a history of marijuana use, including marijuana-containing food and beverages, regardless of the amount or type of cannabis used.

The required sample size was estimated using a formula for two independent proportions and with

consideration of prior research. For instance, in a previous study, it was found that 17% of the non-teenage pregnant women in the study had a history of illicit drug use[9]. We therefore expected about 34% of the teenage pregnant women would have a history of illicit drug use, while the ratio of the non-teenage to teenage pregnant women who attended antenatal care at our institute was around 4:1. To achieve an alpha error of 0.05 and beta error of 0.20, we determined that the sample size required for the non-teenage group and teenage group would be around 236 and 59 participants, respectively, or 295 overall. Allowing for a 5% loss or missing data, approximately total 310 participants were required.

Statistical analysis

The baseline characteristics of the participants within each group were examined and recorded as percentages. The Shapiro–Wilk normality test was used for the normal distribution data, while comparisons of the numbers of participants who had a history of illicit drug use between the teenage and non-teenage groups were performed using the chi-square test or Fisher–Freeman–Halton exact test. Comparisons of the number of participants who had a history of illicit drug use during pregnancy between the teenage and non-teenage groups were also done and the risk factors for predicting illicit drug use during pregnancy were identified using Co-linear test and multiple logistic regression analysis. The prevalence of illicit drug use in the teenage and non-teenage groups before and during pregnancy were recorded and presented as percentages. Lastly, the overall adverse pregnancy, maternal and neonatal adverse outcomes were recorded and presented as percentages and compared between the participants who had a history of illicit drug use and those who did not by chi-square test. In all the statistical tests, p-value < 0.05 was considered statistically significant.

Results

Overall, 310 pregnant women were enrolled in the study, and split into two groups: a teenage group (62 participants) and non-teenage group (248 participants), respectively. The median (interquartile range, IQR) maternal ages in the teenage and non-teenage groups were 19 (18, 19) and 29.5 (26, 33) years old, respectively. All the enrolled participants completed questionnaires to give their personal data. All the participants in the teenage group and non-teenage group were followed until delivery, except for 2 participants in the non-teenage group who spontaneously lost the fetus in the first trimester of pregnancy (Fig. 1).

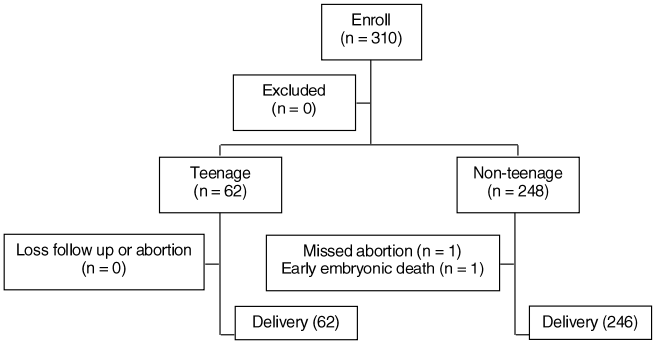

Fig. 1. Flowchart for study inclusion.

Table 1 presents the participants' baseline characteristics in both groups. The participants' religion, occupation, level of education, maternal family status, age at first sexual intercourse, family income, primigravida or nulliparous status, and gestational age at enrollment were analyzed and were

found to be significantly different between both groups. The prevalence of a history of any illicit drug use (alcohol or cigarette smoking or marijuana or amphetamine) before pregnancy was 50/62 (80.6%) in the teenage group and 170/248 (68.5%) in the non-teenage group, respectively.

Table 1. Baseline characteristics of the study participants (n = 310).

Characteristics	Teenage group (n = 62)	Non-teenage group (n = 248)	p value
Religion, n (%)			0.005*
- Buddhist	44 (71%)	215 (86.7%)	
- Muslim	18 (29%)	31 (12.5%)	
- other	0 (0%)	2 (0.8%)	
Race, n (%)			0.432*
- Thai	44 (71%)	193 (77.8%)	
- SEA	18 (29%)	54 (21.8%)	
- other	0 (0%)	1 (0.4%)	
Occupation, n (%)			< 0.001*
- Monthly income	11 (17.7%)	126 (50.8%)	
- Daily income	6 (9.7%)	35 (14.1%)	
- Government officer	0 (0%)	14 (5.6%)	
- Unemployed	45 (72.6%)	73 (29.4%)	
Location, n (%)			0.848*
- Nakhon Nayok & Pathum Thani	56 (90.3%)	227 (91.5%)	
- Bangkok	2 (3.2%)	5 (2%)	
- Others	4 (6.5%)	16 (6.5%)	
Level of education, n (%)			0.030*
- Junior high school or lower	33 (53.2%)	88 (35.5%)	
- Senior high school or higher	29 (46.8%)	157 (63.3%)	
Legal status			0.503*
- Thai citizen	46 (74.2%)	194 (78.2%)	
- legally entered foreigner	11 (17.7%)	43 (17.3%)	
- illegally entered foreigner	5 (8.1%)	11 (4.4%)	
Duration of social media use per day			0.359*
- less than 7 hours	32 (51.6%)	144 (58.1%)	
- more than 7 hours	30 (48.4%)	104 (41.9%)	
Marriage status			0.425**
- stay as couple	59 (95.2%)	241 (97.2%)	
- divorced/widowed	3 (4.8%)	7 (2.8%)	

Table 1. Baseline characteristics of the study participants (n = 310). (Cont.)

Characteristics	Teenage group (n = 62)	Non-teenage group (n = 248)	p value
Maternal family status			< 0.001*
- stay as family	33 (53.2%)	187 (75.4%)	
- broken family	29 (46.8%)	61 (24.6%)	
Multiple sex partners (≥ 2 at the same time)			1.000**
- Yes	1 (1.6%)	4 (1.6%)	
- No	61 (98.4%)	244 (98.4%)	
Age at first sexual intercourse			< 0.001*
- < 15	16 (25.8%)	11 (4.4%)	
- 15–18	45 (72.6%)	125 (50.4%)	
- ≥ 19	1 (1.6%)	112 (45.2%)	
Family income (Baht)			< 0.001*
- < 15,000	27 (43.5%)	48 (19.4%)	
- 15,000–29,999	25 (40.3%)	92 (37.1%)	
- 30,000–50,000	9 (14.5%)	84 (33.9%)	
- > 50,000	1 (1.6%)	24 (9.7%)	
Primigravida, n (%)			< 0.001*
- Yes (G = 1)	53 (85.5%)	90 (36.3%)	
- No (G ≥ 2)	9 (14.5%)	158 (63.7%)	
Nulliparous n (%)			< 0.001*
- yes (P = 0)	59 (95.2%)	115 (46.4%)	
- no (P ≥ 1)	3 (4.8%)	133 (53.6%)	
History of abortion, n (%)			0.071*
- Yes	54 (87.1%)	190 (76.6%)	
- No	8 (12.9%)	58 (23.4%)	
GA			0.002*
- First trimester	10 (16.1%)	27 (10.9%)	
- Second trimester	21 (33.9%)	41 (16.5%)	
- Third trimester	31 (50%)	180 (72.6%)	
STD history			0.795*
- presence	7 (11.3%)	31 (12.5%)	
- absence	55 (88.7%)	217 (87.5%)	

SEA: Southeast Asian, GA: gestational age , STD: sexually transmitted disease
* Pearson chi-square.
** Fisher–Freeman–Halton exact test.

Table 2 presents the details of each illicit drug used before pregnancy, classified by the teenage and non-teenage groups, respectively. During pregnancy, the prevalence of participants who had a history of any illicit drug use (alcohol or cigarette smoking or marijuana or amphetamine) was reduced to 20/62 (32.3%) and 46/248 (18.5%) in the teenage and non-teenage groups, respectively.

Table 3 presents the details of each illicit drug type used during pregnancy, classified by the teenage and non-teenage groups. No participants were diagnosed with alcoholism before or during pregnancy in this study.

Table 2. Prevalence of participants who had a history of each type of illicit drug use before pregnancy according to the teenage and non-teenage groups.

Group	Before pregnancy	Teenage group (n = 62)	Non-teenage group (n = 248)
Alcohol n,(%)	Not use	14 (22.6%)	79 (31.9%)
	Social drinker	23 (37.1%)	102 (41.1%)
	Binge drinker	15 (24.2%)	45 (18.1%)
	Problem drinker	10 (16.1%)	22 (8.9%)
Cigarette n, (%)	Not use	31 (50%)	204 (82.3%)
	Social smoker	0 (0%)	3 (1.2%)
	Regular smoker for less than 3 years	1 (1.6%)	3 (1.2%)
	Regular smoker for more than 3 years	1 (1.6%)	3 (1.2%)
	E-cigarettes smoker	6 (9.7%)	28 (11.3%)
	Smoked before 18 years old	23 (37.1%)	7 (2.8%)
Marijuana uses n, (%)	No	57 (91.9%)	237 (95.6%)
	Yes	5 (8.1%)	11 (4.4%)
Amphetamine uses n, (%)	No	60 (96.8%)	244 (98.4%)
	Yes	2 (3.2%)	4 (1.6%)

Table 3. Prevalence of participants who had a history of each type of illicit drug use during pregnancy according to the teenage and non-teenage groups.

Group	During pregnancy	Teenage group (62)	Non-teenage group (248)
Alcohol n, (%)	Not use	44 (71%)	208 (83.9%)
	Social drinker	7 (11.3%)	17 (6.9%)
	Binge drinker	4 (6.5%)	10 (4%)
	Problem drinker	7 (11.3%)	13 (5.2%)
Cigarette n, (%)	Not use	49 (79%)	235 (94.8%)
	Still smoking	13 (21%)	13 (5.2%)
Marijuana uses n, (%)	No	61 (98.4%)	248 (100%)
	Yes	1 (1.6%)	0 (0%)
Amphetamine uses n, (%)	No	61 (98.4%)	247 (99.6%)
	Yes	1 (1.6%)	1 (0.4%)

Table 4 presents comparisons of the number of participants who had taken illicit drugs during pregnancy (by multiple logistic regression). Being a teenager, less than junior high school status, more than 7-hour social media use per day and age at first sexual intercourse were statistically significantly associated with illicit drug use during pregnancy in univariate analysis. Interestingly, after statistical adjustment, teenage pregnancy was not found to be a factor that reduced the risk of illicit drug use during pregnancy (adjusted odds ratio (OR) 0.716, 95%CI 0.305, 1.682, p = 0.443), while a lower educational level (junior high school or lower), more than 7-hour social media use per day and age at first sexual intercourse were still statistically significantly associated with illicit drug use during pregnancy.

Table 4. Teenage and other possible risk factors for predicting participants who had engaged in illicit drug use during pregnancy.

Variable		Crude OR	95%CI	p value	Adjusted OR	95%CI	p value
Teenager	Yes	2.091	1.123–3.892	0.020	0.716	0.305–1.682	0.443
	No	1	-	-	1	-	-
Occupation	Monthly income	0.547	0.301–0.993	0.047	1.085	0.512–2.300	0.831
	Daily income	0.530	0.214–1.314	0.171	0.586	0.218–1.579	0.291
	Government	0.429	0.091–2.023	0.285	0.621	0.104–3.709	0.601
	Unemployed	1	-	-	1		
Education	Junior high school or lower	2.430	1.398–4.226	0.002	2.651	1.355–5.190	0.004
	Senior high school or higher	1	-	-	1	-	-
Family income	< 15,000	3.451	0.940–12.665	0.062	1.211	0.270–5.431	0.802
	15,000–29,999	1.892	0.522–6.855	0.331	0.838	0.200–3.511	0.808
	30,000–50,000	1.410	0.374–5.315	0.612	0.648	0.149–2.817	0.563
	> 50,000	1	-	-	1	-	-
Nulliparous	Yes	1.613	0.916–2.839	0.098	1.477	0.722–3.022	0.286
	No	1	-	-	1	-	-
Marital status	Divorced/separated	2.559	0.700–9.349	0.155	2.878	0.632–13.096	0.172
	Married/living together	1	-	-	1	-	-
Parent marital status	Divorced/separated	1.541	0.867–2.740	0.141	1.058	0.550–2.035	0.866
	Married/living together	1	-	-	1	-	-
Duration of social media use per day	7 h up	2.092	1.205–3.632	0.009	1.912	1.029–3.552	0.040
	< 7 h	1	-	-	1	-	-
Age at first sexual intercourse	< 15	7.418	2.780–19.793	< 0.001	5.737	1.796–18.332	0.003
	15–19	3.140	1.541–6.397	0.002	3.368	1.509–7.517	0.003
	> 19	1	-	-	1	-	-

OR: odds ratio, CI: confidence interval.

Table 5 presents a comparison of the incidence of adverse maternal outcomes, adverse neonatal outcomes and adverse pregnancy outcomes between the participants who had a history of illicit drug use during pregnancy and those who did not. The incidence of adverse neonatal outcomes (preterm delivery, intrauterine growth restriction, and respiratory problem) was significantly higher in the participants who had a history of illicit drug use than those who did not (33.3% vs 19%, p = 0.013). While the incidences of adverse maternal outcomes (pregnancy-induced hypertension, placental abruption and placenta previa/placenta accreta spectrum) and overall adverse pregnancy outcomes were comparable between both groups. We found that 18/66 (27.3%) of participants used ≥ two types of illicit drug together. 16/18 (88.9%) of participants took combined alcohol with cigarette smoking. When subgroup analysis between participants using each illicit drug individually, did not reveal a statistically significant difference in overall, maternal or neonatal adverse outcomes.

Table 5. Comparison of the incidence of adverse maternal outcomes, adverse neonatal outcomes and adverse pregnancy outcomes between the participants who had a history of illicit drug use during pregnancy and those who did not.

Outcome		History of illicit drug use (n = 66)	No history of illicit drug use (n = 242)	p value
Adverse maternal outcome n, (%)	Yes	14 (21.2%)	50 (20.7%)	0.922*
	PIH	10	33	
	Placental abruption	0	1	
	Placenta previa/PAS	4	16	
	No	52 (78.8%)	192 (79.3%)	
Adverse neonatal outcome n, (%)	Yes	22 (33.3%)	46 (19%)	0.013*
	Preterm delivery	10	19	
	IUGR	6	192 (79.3%)	
	Respiratory problem	6	46 (19%)	
	No	44 (66.7%)	196 (81%)	
Adverse pregnancy outcome n, (%)	Yes	27 (40.9%)	75 (31%)	0.129*
	No	39 (59.1%)	167 (69%)	

PIH: pregnancy induced hypertension, PAS: placenta accreta spectrum, IUGR: intrauterine growth restriction
Respiratory problems: including meconium aspiration syndrome and early neonatal sepsis
*Pearson chi-square

Discussion

Although both teenage pregnancy and illicit drug use are important concerns for obstetricians, few studies have been conducted on either of these topics in Thailand, especially in the past decade[14, 15]. However, in 2002, a study in Bangkok reported that 66 of 44,640 (0.15%) intrapartum pregnant women used amphetamines or derivatives[15]. A later study in 2017 reported the prevalence of alcohol, tobacco and illicit drug use during pregnancy was 5.6% in Southern Thailand[16]. Both these represent a lower prevalence than in our present study. This may be explained by the different times and the diagnostic definition. The latter reported the diagnostic definition based on a questionnaire completed by the study participants, who also reported mental health problems.

According to the baseline characteristics of the participants in the teenage pregnancy group, it was found that the majority of the teenage pregnancy participants in this study were Buddhist, unemployed, had a level of education lower than junior high school, had divorced parents, had a younger age than 18 at first sexual intercourse, an income of less than 30,000 baht, and this was their first time of experiencing pregnancy and delivery (Table 1). These personal characteristics mostly lead to teenage pregnancy being categorized as a problem for those with a low socioeconomic status. From the findings, we also demonstrated that the characteristics of the teenage pregnant women were more compatible with a lower socioeconomic status than those of the non-teenage pregnant women. A previous study reported that a low socioeconomic status also increased the risk of pregnancy complications, such as miscarriage, preterm delivery, preeclampsia and eclampsia[17]. It has been suggested that this is caused by the inadequate prenatal care that low socioeconomic pregnant women may receive[18]. Thus, we suggest that medical healthcare providers should carefully monitor teenage pregnant women with low socioeconomic status and consider them as high-risk pregnancies. Moreover, health services should facilitate them receiving adequate prenatal care.

Next, it was very interesting for the possible factors associating with illicit drug use after univariate analysis, we found that being a teenager, having a regular monthly income, a level of education of junior high school or lower, a duration of social media use of more than 7 hours per day (more than 7 hours per day social media use was found that associated with illicit drug use and mental health consequence)[19], and age at first sexual intercourse of less than 19 years old (i.e., first sexual intercourse at teenage) were all risk factors for illicit drug use during pregnancy. However, when adjusting for each of the factors, the factors that remained as significant factors after adjustment of the OR were a level of education of junior high school or lower, a duration of social media use of more than 7 hours per day, and first sexual intercourse at teenage. This study was consistent with several previous reports that found a relationship between social media/online activity with accessibility to illicit drugs[20, 21]. It is possible that a prolonged duration of social media use per day increases the risk of illicit drug via encountering drug behaviors via that media. However, other previous studies have also found that teenage pregnancy is more likely to be a risk factor for substance use (tobacco, alcohol and marijuana) than non-teenage pregnancy and that depression is associated with persistent tobacco and marijuana use. However, at the time of that study, social media was not as prevalent as it is today[22]. Although it is difficult to separate being a teenager from socioeconomic problems, including social media use, in our opinion, we feel that education can help alleviate the problems. Moreover, it is encouraging that previous studies have found that pregnancy is an effective motivating factor that can prompt teenagers to quit their illicit drug use[23, 24]. Further study on the effectiveness of short courses of education in reducing drug use is warranted. Our study is the most recent report about illicit drug use in reproductive age women in Thailand and during pregnancy. Moreover, we also inquired about the four main types of illicit drugs of interest (cigarette, alcohol, marijuana and amphetamine) and also categorized drug users by their behavior characteristics, and frequency and duration of drug exposure, which could help medical providers to determine the possibility of an illicit drug effect on the physical and mental health of users. This is a key strength of study. Lastly, the types of adverse maternal or neonatal outcomes were similar to those observed in both teenage pregnancies and illicit drug use pregnancies[11, 25-27]. However, our study found that only adverse neonatal outcomes (preterm delivery, intrauterine growth restriction, and respiratory problems) were significantly associated with illicit drug use during pregnancy. It is similar to the previous study that abused amphetamine was more likely to develop anemia, preterm delivery, thick meconium-stained amniotic fluid and delivered small for gestational age neonates[28]. We found no significant association

between the overall and maternal adverse outcomes (pregnancy induced hypertension, placental abruption and placenta previa/placenta accreta spectrum) with illicit drug use during pregnancy. The explanation for this difference was that our sample size may have been too small to come to a firm conclusion on these outcomes, and so we suggest this should be investigated further in a future study.

The study was conducted as a prospective cross-sectional that based on our interview. Only two interviewers who were given standardized training and attempted to use similar questions, were a strength of this study. However, the limitation of this study was that no laboratory test to confirm the use or not of illicit drugs. If the laboratory confirmation was performed, the reliability of the illicit drugs use should be improved. The number of sample size using each illicit drug individually was limited to clearly determine the specific effect on adverse outcomes.

Conclusion

Prevalence of illicit drug use during pregnancy in teenage was not different from in non-teenage. Teenagers alone were not at risk of engaging in illicit drug use. The level of education of junior high school or lower, more than 7 hours per day social media use, and first sexual intercourse at teenage were significant factors associated with a higher prevalence of illicit drug use during pregnancy. Our interview-based study found a higher prevalence of illicit drug use during pregnancy (alcohol, tobacco, marijuana and amphetamine). We also found that teenage pregnant women were more likely to have a low socioeconomic status.

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Author Contribution

CK: protocol/project development, Data collection or management, Data analysis, Manuscript writing

KK: protocol/project development, Data analysis, Manuscript editing

TH: protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Correlation of Total Dosage and Duration of Magnesium Sulfate Administration in Pregnant Women Associated with Magnesium Levels in Umbilical Cord Blood

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ABSTRACT

Objectives: To evaluate the correlation between the total dosage and duration of maternal magnesium sulfate ($MgSO_4$) administration and umbilical cord blood magnesium levels, and to determine clinically useful cutoff values associated with elevated neonatal magnesium concentrations.

Materials and Methods: The cross-sectional study included 47 pregnant women ≥ 24 weeks' gestation who received $MgSO_4$ following the regimen of loading dose 4 grams, followed by a maintenance dose of 2 gram/hour intravenously at Rajavithi Hospital. Maternal serum magnesium was collected within 1 hour before delivery, and umbilical cord blood samples were obtained immediately after placenta delivery. Total $MgSO_4$ dose, infusion duration, and biochemical parameters were recorded. Pearson's correlation, linear regression, and receiver operating characteristic (ROC) curve analysis were performed.

Results: Total dosage of $MgSO_4$ and infusion duration showed significant positive correlations with cord blood magnesium levels ($r = 0.65$, $p < 0.001$). Maternal serum magnesium demonstrated the strongest correlation ($r = 0.73$, $p < 0.001$) and remained an independent predictor in the multivariable model together with maternal serum creatinine. ROC analysis identified two clinically useful cutoff values for predicting cord magnesium ≥ 5 mg/dL: a total dose of 12.8 g (sensitivity 100%, specificity 71.4%) and an infusion duration of 280 minutes (sensitivity 100%, specificity 68.6%). A higher level of exposure, corresponding to 31.3 g of total dose or 855 minutes of infusion, yielded 100% specificity.

Conclusion: Both the total dosage of $MgSO_4$ and infusion duration were strong predictors of neonatal cord blood magnesium levels. The identified cutoff values provided practical guidance for assessing the risk of elevated neonatal magnesium exposure and support targeted newborn surveillance following maternal $MgSO_4$ therapy.

Keywords: magnesium sulfate, umbilical cord blood, pregnancy.

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ความสัมพันธ์ของปริมาณทั้งหมดและระยะเวลาในการให้แมกนีเซียมซัลเฟตในหญิงตั้งครรภ์ ที่สัมพันธ์กับระดับแมกนีเซียมในเลือดจากสายสะดือ

สโรชา ปริยานนท์, ปรุฬห์ สนุ่นรัตน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินความสัมพันธ์ระหว่างปริมาณทั้งหมดและระยะเวลาในการให้ยาแมกนีเซียมซัลเฟตของมารดากับระดับแมกนีเซียมในเลือดสายสะดือ และเพื่อหา Cutoff ที่มีความหมายทางคลินิกที่สัมพันธ์กับระดับแมกนีเซียมทารกแรกเกิดที่สูง*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวาง รวมหญิงตั้งครรภ์ 47 ราย อายุครรภ์ ≥ 24 สัปดาห์ซึ่งได้รับแมกนีเซียมซัลเฟตตามแนวทางการให้ยาปริมาณเริ่มต้น 4 กรัม และให้คงระดับขนาด 1 กรัมต่อชั่วโมงทางหลอดเลือดดำที่โรงพยาบาลราชวิถี เลือดมารดาสำหรับวัดแมกนีเซียมถูกเก็บภายใน 1 ชั่วโมงก่อนคลอด และเลือดสายสะดือถูกเก็บทันทีหลังรกคลอด มีการบันทึกขนาดยารวม ระยะเวลาให้ยา และพารามิเตอร์ทางชีวเคมี มีการวิเคราะห์สหสัมพันธ์ การถดถอย และ receiver operating characteristic (ROC) curve*

ผลการศึกษา: *ปริมาณทั้งหมดของแมกนีเซียมซัลเฟตและระยะเวลาในการให้ยา แสดงความสัมพันธ์เชิงบวกอย่างมีนัยสำคัญ กับระดับแมกนีเซียมในเลือดสายสะดือ ($r = 0.65$, $p < 0.001$) ระดับแมกนีเซียมในเลือดของมารดา แสดงความสัมพันธ์ที่สูงที่สุด ($r = 0.73$, $p < 0.001$) และยังคงเป็นปัจจัยทำนายอิสระในแบบจำลองหลายตัวแปร ร่วมกับระดับครีอะตินีนของมารดา การวิเคราะห์ ROC ระบุ cutoff ที่มีความหมายเชิงคลินิกสองค่า สำหรับการทำนายระดับแมกนีเซียมในสายสะดือที่ ≥ 5 mg/dL ได้แก่ ขนาดยารวม 12.8 กรัม (ความไวร้อยละ 100 ความจำเพาะร้อยละ 71.4) และระยะเวลาให้ยา 280 นาที (ความไวร้อยละ 100 ความจำเพาะร้อยละ 68.6) ระดับการได้รับยาที่สูงกว่า ซึ่งเทียบเท่ากับขนาดยารวม 31.3 กรัม หรือระยะเวลาให้ยา 855 นาที ให้ค่าความจำเพาะร้อยละ 100*

สรุป: *ทั้งขนาดยาแมกนีเซียมซัลเฟตรวมและระยะเวลาให้ยา เป็นตัวทำนายที่สำคัญของระดับแมกนีเซียมสายสะดือทารก ค่า cutoff ที่ระบุได้ให้แนวทางที่สามารถใช้จริงในคลินิก สำหรับประเมินความเสี่ยงของแมกนีเซียมสูงในทารก และสนับสนุนการเฝ้าระวังทารกแรกเกิดอย่างเฉพาะเจาะจงหลังมารดาได้รับแมกนีเซียมซัลเฟตของ*

คำสำคัญ: *แมกนีเซียมซัลเฟต, เลือดจากสายสะดือ, การตั้งครรภ์*

Introduction

Magnesium sulfate ($MgSO_4$) has been widely utilized in obstetrics for various clinical indications. It is most commonly administered for the prevention of seizures in pregnant women with hypertensive disorders or preeclampsia. Additionally, it is used as a tocolytic agent to inhibit uterine contractions and as a neuroprotective agent for preterm neonates[1-3].

The use of magnesium sulfate during the peripartum period has become increasingly common, as magnesium ions can cross the placenta and are rapidly absorbed into fetal tissues[4]. A previous study, however, found that maternal administration of magnesium sulfate is the most common cause of neonatal magnesium toxicity. Following intravenous administration in pregnant women, approximately 40% of circulating magnesium ions bind to plasma proteins, while the unbound fraction distributes into the extravascular extracellular compartment or, various maternal tissues, crossing the placenta into the fetal tissues and amniotic fluid[5, 6].

Magnesium exerts its pharmacologic effect primarily by inhibiting acetylcholine release at the neuromuscular junction, particularly affecting the respiratory muscles, although it does not have a direct central nervous system effect. Specifically, magnesium sulfate reduces the amount of acetylcholine released, decreases the sensitivity of the postsynaptic membrane, and inhibits muscle membrane excitability, resulting in muscle weakness and respiratory depression[7].

Neonatal outcomes following maternal magnesium sulfate administration warrant close monitoring, even though, the effects of magnesium sulfate on neonates remain unclear. Several studies have reported elevated serum magnesium levels in neonates whose mothers received magnesium sulfate during pregnancy[8-10]. Furthermore, neonates exposed to antenatal magnesium sulfate may develop hypermagnesemia, respiratory depression, apnea, cyanosis, decreased muscle tone (hypotonia), low apgar scores and increased rates of neonatal intensive care unit (NICU) admission and length of stay (LOS)[9, 11-14]. Neonatal magnesium sulfate levels above 2.5 mmol/L (~ 6.08 mg/dL) may increase the risk of hypotonia, respiratory depression, and NICU admission[15, 16]. Umbilical cord blood magnesium levels exceeding 4.5 mEq/L (~5.4 mg/dL) are associated with a higher risk of immediate neonatal death.

A recent study demonstrated a significant positive correlation between the cumulative dose of magnesium sulfate and maternal serum magnesium levels with cord blood magnesium levels in neonates[17]. Cord blood samples may be collected from either the umbilical artery or vein, as the magnesium concentrations in both vessels have been shown to be comparable[18]. In this study, samples were collected from the umbilical vein due to its larger size and ease of identification.

The primary objective of this research was to investigate the correlation between the total dose and duration of magnesium sulfate administration during pregnancy before delivery and the umbilical cord blood magnesium levels in neonates. The secondary objective was to find the cutoff of cumulative dose $MgSO_4$ and the duration of $MgSO_4$ administration that will cause cord blood magnesium level ≥ 5mg/dL which our research assumed that this value may cause poor neonatal outcomes. The findings aim to support neonatal surveillance and preparedness for potential complications associated with hypermagnesemia after birth.

Materials and Methods

This was a cross-sectional study conducted at Rajavithi Hospital between July 2024 and June 2025. The study was registered with the Research Ethics Committee of Rajavithi Hospital (Reference number 131/2567, issue on June 25th, 2024) before data collection started. The inclusion criteria were women with singleton pregnancy ≥ 24 weeks gestation who

received intravenous magnesium sulfate before delivery, were aged ≥ 18 years, and had an understanding of written or spoken Thai. The exclusion criteria were pregnant people who had renal impairment (serum creatinine > 1.0 mg/dL) and failure to collect cord blood. All participants provided informed consent. $MgSO_4$ was used for treatment according to obstetric indications (such as prevention of eclampsia, inhibition of labor, and fetal neuroprotection). All patients received a standard loading dose of $MgSO_4$ 4 g, followed by a continuous infusion at 2g/h until delivery. The cumulative dose of $MgSO_4$ before delivery was calculated as the sum of the loading dose and the total amount given during the maintenance infusion, using the following formula: Cumulative dose (g) = loading dose (g) + [infusion rate (g/h) x infusion duration (h)]. The duration of $MgSO_4$ infusion was defined as the time from administration of the loading dose until delivery. In cases with interruptions or multiple infusion segments, each segment was calculated separately and summed. Any additional bolus doses were also included in the total cumulative dose. Maternal bloods for magnesium levels were collected within 1 hour before delivery[23]. Umbilical cord bloods were collected immediately from the umbilical vein, in the part that connects to the placenta, after placental delivery, and amounts of 4-6 ml were then immediately sent for magnesium level testing. All magnesium serums were analyzed using the Alinity ci-series Operation Manual. Baseline characteristics, including obstetric data, total dosage, and duration of $MgSO_4$ were recorded, along with neonate data.

The sample size was calculated based on the formula for correlation coefficient analysis. A previous study by Ahmed Altraigey et al[17] was used as a reference, in which the correlation coefficient (r) was reported as 0.65. With a significance level (α) set at 0.01 and a statistical power of 99%, the sample size was determined to be 47 participants.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corporation, Armonk, NY). Descriptive statistics, including mean, standard deviation, number, and percentage were used to describe baseline characteristics and related data. Pearson's correlation and linear regression were used to determine the correlation between total dosage of $MgSO_4$ and cord blood magnesium, and a p value < 0.05 was considered to be statistically significant.

Results

Forty-seven pregnant women were enrolled. Table 1 shows the baseline characteristics of the participants, whose mean maternal age was 30.5 ± 7.6 years. The average gestational age at delivery was 35.1 ± 3.4 weeks, indicating that the majority of participants (61.7%) delivered preterm (< 37 weeks). Mean BMI was 30.6 ± 5.8 kg/m², and the mean birth weight was 2,201.3 ± 738.8 grams, reflecting the high proportion of preterm births.

More than half of the women (55.3%) were nulliparous, and the vast majority (87.2%) delivered via cesarean section.

Table 2 shows that the median total dosage of $MgSO_4$ was 12.3 grams and the median duration of $MgSO_4$ infusion was 280 minutes. Maternal serum magnesium levels at delivery averaged 5.3 ± 1.6 mg/dL, while umbilical cord blood magnesium levels were slightly lower, with a mean of 4.4 ± 1.1 mg/dL (range 2.9-7.2 mg/dL).

As shown in Table 3, the total dosage of $MgSO_4$ and duration of $MgSO_4$ infusion showed a strong positive correlation with umbilical cord blood magnesium levels ($r = 0.65$, $p < 0.01$). Maternal serum magnesium levels were highly predictive of cord blood levels ($r = 0.73$, $p < 0.01$). Fig. 1 and Fig. 2 illustrate significant positive linear correlations between maternal $MgSO_4$ exposure and umbilical cord blood magnesium levels. Increasing total $MgSO_4$ dosage (Fig. 1) and longer infusion duration (Fig. 2) were both associated with higher cord magnesium concentrations.

Table 1. Baseline characteristics of pregnant women and neonates (n = 47).

Characteristics	mean ± SD (min-max)
Maternal age (years)	30.5 ± 7.6 (18 - 45)
Gestational age (weeks)	35.1 ± 3.4 (26.4 - 40.0)
Body mass index (kg/m^2)	30.6 ± 5.8 (21.9 - 49.6)
Parity, n (%)	
Nulliparity	26 (55.3)
Multiparity	21 (44.7)
Indication for $MgSO_4$ administer, n (%)	
Hypertension in pregnancy	47 (100)
Route of delivery, n (%)	
Vaginal delivery	6 (12.8)
Cesarean delivery	41 (87.2)
Neonate characteristics	
Birth weight (g)	2,201.3 ± 738.8
Preterm (GA < 37 weeks), n (%)	29 (61.7)
Term (GA ≥ 37 weeks), n (%)	18 (38.3)

$MgSO_4$: magnesium sulfate, SD: standard deviation

Table 2. Characteristics of magnesium sulfate administration and serum biochemical levels.

	median (IQR)	min - max
Total dosage of $MgSO_4$ (g)	12.3 (8.64 - 17.98	5.6 - 143.8
Duration of $MgSO_4$ administration (minutes)	280 (162.5 - 444.5)	78 - 4212
	mean ± SD	min - max
Maternal serum magnesium (mg/dL)	5.3 ± 1.60	1.8 - 12.2
Cord blood magnesium (mg/dL)	4.4 ± 1.1	2.9 - 7.2
Maternal serum creatinine (mg/dL)	0.63 ± 0.19	0.4 - 1.1

$MgSO_4$: magnesium sulfate, IQR: interquartile range, SD: standard deviation.

Table 3. Correlation between umbilical cord blood magnesium and total dosage of $MgSO_4$ as well as duration of $MgSO_4$ infusion.

Parameters	Correlation (r)	p value
Total dosage of $MgSO_4$	0.65	< 0.01
Duration of $MgSO_4$ infusion	0.65	< 0.01
Maternal serum magnesium	0.73	< 0.01

$MgSO_4$: magnesium sulfate

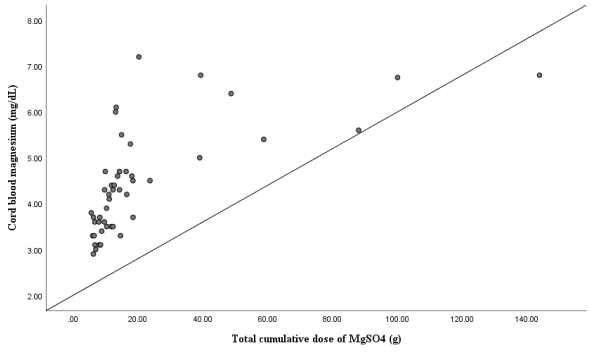

Fig. 1. Scatter plot with regression line showing the relationship between total dosage of $MgSO_4$ and cord blood magnesium levels.

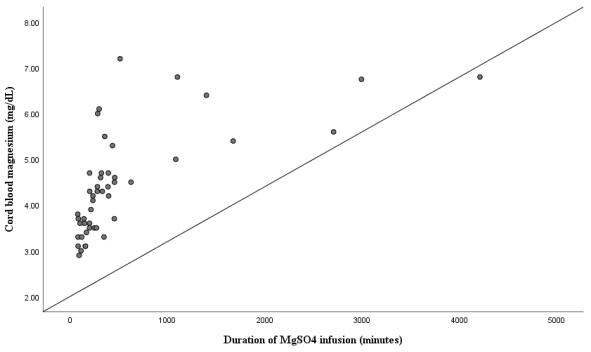

Fig. 2. Scatter plot with regression line showing the relationship between duration of $MgSO_4$ administration and cord blood magnesium levels.

Table 4 presents that total dosage of $MgSO_4$, duration of $MgSO_4$ administration, maternal serum magnesium levels, and maternal serum creatinine were significantly associated with cord blood magnesium level in univariable analysis ($p < 0.01$).

In the multiple linear regression model after adjusting for maternal serum magnesium, birth weight, and creatinine, total dosage of $MgSO_4$ remained a significant predictor of cord blood magnesium levels (Adjusted $\beta = 0.02$, 95% CI 0.01, 0.03, $p < 0.01$), maternal serum magnesium (Adjusted $\beta = 0.28$, 95% CI 0.14, 0.42, $p < 0.01$) and maternal serum creatinine (Adjusted $\beta = 1.98$, 95% CI 0.92, 3.03, $p = 0.001$) remained significantly associated with cord blood magnesium level.

Table 4. Univariable and multivariable linear regression for risk factors for cord blood magnesium level.

Variables	Univariable analysis			Multivariable analysis		
	Crude β	95% CI	p value	Adjusted β	95% CI	p value
Total dosage of $MgSO_4$ (g)	0.03	0.02, 0.04	< 0.001*	0.02	0.01-0.03	< 0.01*
Duration of $MgSO_4$ (hours)	0.05	0.04, 0.07	< 0.001*			
Maternal serum Mg level (mg/dL)	0.52	0.37, 0.66	< 0.001*	0.28	0.14-0.42	< 0.01*
Serum Cr (mg/dL)	2.79	1.17, 4.40	0.001*	1.98	0.92-3.03	0.001*
Maternal BMI (kg/m^2)	-0.02	-0.08, 0.04	0.501			
Birth weight (g)	-0.00	-0.00, 0.00	0.018*	0.00	0.00-0.00	0.790

Adjusted for duration of $MgSO_4$, maternal Mg level and maternal creatinine.

$MgSO_4$: magnesium sulfate, Mg: magnesium, Cr: creatinine, BMI: body mass index, CI: confidence interval

*Significant at $p < 0.05$

Receiver operating characteristic (ROC) analysis demonstrated that both total dose and duration of $MgSO_4$ administration were strong predictors of elevated cord magnesium levels (≥ 5 mg/dL). The ROC curve for total $MgSO_4$ dose demonstrated excellent discriminative ability, with an area under the curve (AUC) of 0.926 (95% CI 0.850, 1.000, $p < 0.001$). The optimal cutoff point, based on the Youden Index, was identified at 12.80 grams (a sensitivity of 100% and specificity of

71.4%) and 31.37 grams (a sensitivity of 58.5% and specificity of 100%) (Fig. 3, Table 5). The ROC curve for duration of $MgSO_4$ infusion also showed strong predictive performance, with an AUC of 0.919 (95% CI 0.836, 1.000, $p < 0.001$). The optimal cutoff point was 280 minutes (a sensitivity of 100% and specificity of 68.6%) and 855 minutes (a sensitivity of 58.6% and specificity of 100%) (Fig. 3, Table 6). These findings suggested that both total dose and duration of $MgSO_4$ administration were accurate predictors of elevated neonatal magnesium exposure.

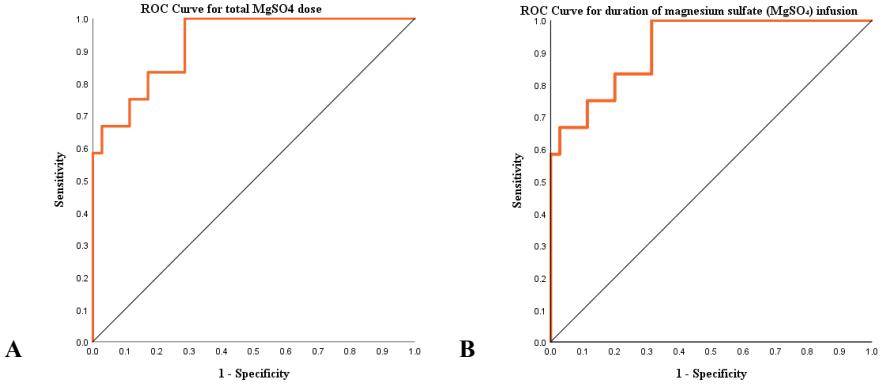

Fig. 3. Cutoff values of total dosage of $MgSO_4$ for predicting cord blood magnesium ≥ 5 mg/dL.

Table 5. Cutoff values of total dosage of $MgSO_4$ for predicting cord blood magnesium ≥ 5 mg/dL.

Cutoff (g)	Sensitivity	Specificity	Positive likelihood ratio
12.80	100.0	71.4	3.50
31.37	58.5	100.0	∞

Table 6. Cutoff values of duration of $MgSO_4$ infusion for predicting cord blood magnesium ≥ 5 mg/dL.

Cutoff (minutes)	Sensitivity	Specificity	Positive likelihood ratio
280	100.0	68.6	3.18
855	58.6	100.0	∞

ROC curves for (A) total dosage of $MgSO_4$ and (B) duration of $MgSO_4$ infusion in predicting elevated umbilical cord serum magnesium level ≥ 5 mg/dL. Both parameters demonstrated excellent predictive performance, with AUC values of 0.919 and 0.926 respectively.

Discussion

This study demonstrated a strong positive correlation between both the total dosage and duration of $MgSO_4$ administration and umbilical cord blood magnesium levels. These findings were consistent with those of previous studies in the literature, including the work by Ahmed Altraigey et al[17], which reported similar trends in elevated cord magnesium concentrations in neonates exposed to antenatal $MgSO_4$ therapy.

Our data further support the hypothesis that transplacental transfer of magnesium is dose-dependent and influenced by the duration of maternal

exposure[4,17].

In this study, the mean cord blood magnesium concentration was 4.4 ± 1.1 mg/dL, aligning with prior reports of neonates exposed to antenatal magnesium sulfate. Large-scale studies, including the BEAM trial, have documented average levels of between 3.7 and 4.4 mg/dL, particularly in the context of neuroprotection for preterm birth[19, 17]. Clinically, serum magnesium concentrations up to 2.0 mmol/L (~ 4.8 mg/dL) in neonates are generally considered safe and well tolerated[3, 21]. Although there is no universally accepted cutoff to define hypermagnesemia in neonates, several studies suggest that levels above 2.5 mmol/L (~ 6.08 mg/dL) may increase the risk of hypotonia, respiratory depression, and NICU admission[15,16]. One study by Basu et al[22] found that cord blood magnesium levels exceeding 4.5 mEq/L (~ 5.4 mg/dL) were associated with a 16.9-fold increased risk of immediate neonatal death. Considering the standard deviation in our data, it is plausible that a subset of neonates had magnesium concentrations exceeding this threshold, warranting attention. Therefore, this study adopted a cutoff value of cord blood magnesium ≥ 5 mg/dL as a potential threshold associated with adverse neonatal outcomes, based on both prior clinical evidence and the distribution of cord blood magnesium levels observed in our own cohort.

This study demonstrated that both the total dose and the duration of antenatal magnesium sulfate ($MgSO_4$) infusion were strongly associated with elevated cord blood magnesium levels (≥ 5 mg/dL), which may potentially increase the risk of adverse neonatal outcomes. ROC curve analysis revealed excellent discriminatory performance of both predictors.

With regard to the total $MgSO_4$ dose, AUC was 0.926, indicating high accuracy in predicting elevated cord magnesium levels. Similarly, the duration of $MgSO_4$ infusion yielded an AUC of 0.919, which also reflects excellent predictive ability. These findings suggested that both cumulative exposure and infusion time were reliable indicators of fetal magnesium transfer.

Our findings indicated that a cutoff value of approximately 12.80 grams for the total $MgSO_4$ dose and 280 minutes for infusion duration may serve as an early threshold for clinical consideration. Furthermore, when maternal cumulative exposure exceeds 31.3 grams or the infusion duration reaches 855 minutes or longer, neonatal serum magnesium level monitoring becomes necessary. These thresholds hold clinical significance, especially in contexts where prolonged $MgSO_4$ exposure is anticipated or when there is a concern regarding neonatal hypermagnesemia, emphasizing the importance of postnatal biochemical surveillance in infants identified as at risk.

Furthermore, within the scope of our research, umbilical cord magnesium levels equal to or exceeding 5 mg/dL can be predicted using the following equation:

Calculated umbilical cord magnesium = 1.268 + [1.976 x serum creatinine (mg/dL)] + [0.729 x serum magnesium (mg/dL)] + [0.019 x total magnesium dosage (grams)]

The calculated umbilical cord magnesium showed a robust positive correlation with the actual measured umbilical cord magnesium ($r = 0.83$, $p < 0.01$). ROC curve analysis indicated that a calculated umbilical cord magnesium threshold of 7.4 can effectively identify cases with true umbilical cord blood magnesium levels of 5 mg/dL or higher, with a sensitivity of 91.7% and a specificity of 94.3% (AUC of 0.96).

A key strength of this study lies in its prospective design and the use of direct biochemical measurements from both maternal serum and umbilical cord blood. The analysis comprehensively evaluated total dosage and duration of magnesium sulfate administration, alongside maternal renal function, as potential predictors of cord blood magnesium levels. The inclusion of both univariate and multivariate regression models enhances the robustness of the findings by accounting for potential confounders.

The limitation of this study was the relatively

small sample size, which restricted our ability to demonstrate a definitive association between maternal $MgSO_4$ dose or duration of infusion and neonatal outcomes. Nevertheless, the study provides meaningful preliminary guidance for clinical practice and highlights the need for future studies with larger cohorts to validate and refine these observations.

Conclusion

Total dose and duration of magnesium sulfate infusion were strong predictors of neonatal cord blood magnesium levels. Importantly, our study identified preliminary clinically meaningful thresholds: 12.8 g total dose and 280 minutes of infusion as early indicators, and 31.3 g or 855 minutes as critical points warranting neonatal monitoring. These findings provide practical guidance for clinicians and highlight the need for future studies with larger cohorts to validate and refine these cutoffs for safer perinatal management.

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Author Contribution

CK: protocol/project development, Data collection or management, Data analysis, Manuscript writing

KK: protocol/project development, Data analysis, Manuscript editing

TH: protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Prevalence and Associated Factors of Endometrial Hyperplasia and Endometrial Cancer in Women with Abnormal Uterine Bleeding and Body Mass Index less than 30 kg/m^2 at Charoenkrung Pracharak Hospital

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ABSTRACT

Objectives: The primary objective was to determine the prevalence and the associated risk factors of endometrial hyperplasia and endometrial cancer in women with abnormal uterine bleeding (AUB) and body mass index (BMI) less than 30 kg/m^2

Materials and Methods: A cross-sectional retrospective study was conducted. The medical records of women with AUB and BMI less than 30 kg/m^2 who underwent endometrial sampling or fractional curettage or hysteroscopy with endometrial biopsy from January 1, 2018 to December 31, 2023 were reviewed. The demographic data included age, parity, BMI, menopause, diabetes mellitus, hypertension, tamoxifen used and histopathological reports were collected. The data were analyzed to determine the prevalence of endometrial hyperplasia and endometrial cancer, and multivariate logistic regression were utilized to identify associated risk factors.

Results: Of all 226 women were recruited. The prevalence of endometrial hyperplasia and endometrial cancer was total 9.2%. In multivariate logistic regression analysis, postmenopause (adjusted odds ratio (aOR) 9.39, 95% CI 1.56, 56.71, p = 0.015) and woman older than 60 years old (aOR 12.27, 95% CI 1.93, 78.20, p = 0.008) were independently associated with endometrial hyperplasia and endometrial cancer.

Conclusion: Postmenopause was an important factor for endometrial hyperplasia and endometrial cancer in women with AUB and BMI less than 30 kg/m^2, risk increasing significantly in those aged over 60 years. Early detection strategies should be considered.

Keywords: prevalence, risk factors, body mass index less than 30 kg/m^2, endometrial hyperplasia, endometrial cancer.

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ความชุกและปัจจัยที่มีความสัมพันธ์กับภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก ในสตรีที่มีเลือดออกผิดปกติจากโพรงมดลูกและมีดัชนีมวลกายน้อยกว่า 30 กก./ม^2 ณ โรงพยาบาลเจริญกรุงประชารักษ์

จิดาภา ฉันทวานิช, ปิยธิดา ทองรอง, จิรพร เหลืองเมตตากุล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยที่มีความสัมพันธ์ของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก ในสตรีที่มีเลือดออกผิดปกติจากโพรงมดลูกและมีดัชนีมวลกายน้อยกว่า 30 กก./ม^2*

วัสดุและวิธีการ: *การศึกษาข้อมูลแบบย้อนหลัง โดยทบทวนเวชระเบียนของสตรีที่มาด้วยอาการเลือดออกผิดปกติจากโพรงมดลูกและมีดัชนีมวลกายน้อยกว่า 30 กก./ม^2 ที่ได้รับการเก็บตัวอย่างชิ้นเนื้อจากโพรงมดลูกด้วยวิธีดูดเก็บเยื่อบุโพรงมดลูก หรือขูดมดลูกแบบแยกส่วน หรือการวินิจฉัยโดยใช้กล้องส่องโพรงมดลูกและเก็บตัวอย่างเยื่อบุโพรงมดลูกส่งตรวจ ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2561 ถึง 31 ธันวาคม พ.ศ. 2566 รวบรวมข้อมูลพื้นฐานของผู้ป่วย ประกอบด้วย อายุ จำนวนการคลอดบุตร ดัชนีมวลกาย ภาวะวัยหมดประจำเดือน โรคเบาหวาน โรคความดันโลหิตสูง ประวัติการใช้ยา tamoxifen และรายงานทางพยาธิวิทยาของเยื่อบุโพรงมดลูกที่ได้รับการตรวจ จากนั้นนำข้อมูลมาวิเคราะห์หาความชุกของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก รวมถึงวิเคราะห์แบบถดถอยโลจิสติกพหุตัวแปรเพื่อหาปัจจัยที่มีความสัมพันธ์ในการเกิดโรค*

ผลการศึกษา: *จากสตรีทั้งหมด 226 ราย พบความชุกของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูกคิดเป็นร้อยละ 9.2 จากการวิเคราะห์แบบถดถอยโลจิสติกพหุตัวแปรพบว่า ภาวะวัยหมดประจำเดือน (adjusted odds ratio (aOR) 9.39, 95% CI 1.56, 56.71, p = 0.015) และ อายุมากกว่า60 ปี (aOR 12.27, 95% CI 1.93, 78.20, p = 0.008) เป็นปัจจัยที่มีความสัมพันธ์กับการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก*

สรุป: *ภาวะวัยหมดประจำเดือนเป็นปัจจัยที่มีความสำคัญในการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก ในสตรีที่มีเลือดออกผิดปกติจากโพรงมดลูกและมีดัชนีมวลกายน้อยกว่า 30 กก./ม^2 ความเสี่ยงเพิ่มขึ้นอย่างมีนัยสำคัญตามอายุ โดยเฉพาะอายุมากกว่า 60 ปี ดังนั้นควรพิจารณาแนวทางการค้นหาตั้งแต่ระยะแรก*

คำสำคัญ: *ความชุก, ปัจจัยเสี่ยง, ดัชนีมวลกายน้อยกว่า 30 กก./ม^2, ภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ, มะเร็งเยื่อบุโพรงมดลูก*

Introduction

Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine cavity with abnormal volume, duration, frequency, or regularity of menstrual cycles[1]. It is a common gynecologic condition, affecting approximately 10–30% of women[2]. AUB has multiple various etiologies, including structural causes such as endometrial polyps, endometrial hyperplasia, and endometrial carcinoma, while non-structural causes include hormonal imbalance. Endometrial hyperplasia and carcinoma have been reported in up to 20% of women with AUB[3-5].

The International Agency for Research on Cancer (IARC), GLOBOCAN 2022, reported 420,368 new cases of endometrial cancer and 97,723 deaths worldwide. In Thailand, it is the second most common gynecologic malignancy after cervical cancer, with 4,248 new cases and 1,301 deaths annually[6]. Endometrial cancer most frequently occurs in women aged 60–70 years, with about 95% diagnosed after the age of 40[7]. Endometrial hyperplasia, often resulting from hormonal imbalance such as unopposed estrogen, is recognized as a precursor lesion with potential progression to endometrial carcinoma[8].

Previous studies have shown varying prevalence and associated risk factors of endometrial hyperplasia and endometrial carcinoma (EH/EC) in women with AUB. Obesity (body mass index (BMI) more than 30 kg/m²) has consistently been identified as an important risk factor. However, several reports demonstrated that even among women with BMI less than 30 kg/m², the prevalence of EH/EC ranged from 4% to 15.7%[9-16]. Most studies focused on low risk or premenopausal populations, and few specifically examined women with BMI less than 30 kg/m² [9,12]. This group remains underrecognized despite its clinical importance. Moreover, no such study has been conducted in hospitals under the Bangkok Metropolitan Administration (BMA).

Charoenkrung Pracharak Hospital is a tertiary-care center. Women presenting with AUB would be evaluate using various modalities, including endocervical sampling, fractional curettage, office hysteroscopy, and hysteroscopy with biopsy. Treatment was provided by general gynecologists, gynecologic oncologists and gynecologic endoscopist allowing early specialist evaluation for appropriate management of AUB.

Based on these data, the objective of the present study was to determine the prevalence and associated risk factors of EH/EC among women with AUB and BMI less than 30 kg/m².

Materials and Methods

This retrospective cross-sectional study was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (BMAHREC) (R007hc/67_EXP). We enrolled women who presented with AUB and BMI less than 30 kg/m², who underwent endometrial tissue diagnosis at Charoenkrung Pracharak Hospital from January 1, 2018 to December 31, 2023. The sample size was calculated for cross-sectional study using a 15.71% prevalence of EH/EC in women with AUB and BMI less than 30 kg/m², based on study in 2019(11), with a 95% confidence level, acceptable error 0.05 and an additional 10% adjustment for potential data loss, resulting in a required sample size of 226 participants.

Between 2018 and 2023, a total of 2,782 women presented with AUB at Charoenkrung Pracharak Hospital. Of these, 1,012 women with BMI less than 30 kg/m². Based on the sample size calculation described above, a total of 226 participants were required for the study. Systematic random sampling was employed in order to reduce selection bias.

The inclusion criteria were women aged from 20 to 80 years, presented with AUB and BMI less than 30 kg/m² who underwent endometrial evaluation including endometrial sampling, fractional curettage or hysteroscopy with biopsy and had confirmed histopathological results. In Charoenkrung pracharak

hospital, indications for endometrial evaluation included age more than 35 years, or age less than 35 years with one or more risk factors, including polycystic ovary syndrome, chronic anovulation, a family history of endometrial or colorectal cancer, persistent or recurrent AUB despite medical treatment, or tamoxifen used. Ultrasonography for endometrial assessment was not routinely performed in all women with AUB and was selectively performed according to clinical indications and patient risk stratification. The exclusion criteria were inadequate tissue for histopathological diagnosis, a prior diagnosis of EH/EC, and presence of other malignancies with uterine metastasis.

Data was collected using case record forms, coded without patient identifiers, and stored in a password-protected computer accessible only to the investigators. The variables collected included baseline characteristics (age, nationality, BMI, parity, menopausal status, history of tamoxifen use, diabetes mellitus, hypertension, smoking status, family history of breast or colorectal cancer), and pathological outcomes from endometrial sampling or fractional curettage or hysteroscopy with endometrial biopsy. Diagnoses of endometrial hyperplasia and endometrial cancer were independently reviewed by two pathologists in accordance.

Data analysis was performed using SPSS version 26. Continuous variables were presented as mean with standard deviation or median and interquartile range. Categorical variables were presented as number with percentage. Descriptive statistics were used to present the prevalence of EH/EC. Multivariable logistic regression analysis was used to analyze the associating factors and presented as adjusted odds ratios (aOR) and 95% confidence intervals (CI). A p value < 0.05 was considered statistically significant.

Results

From January 2018 to December 2023, 226 participants met the inclusion criteria. Of the total participants, 182 (80.5%) underwent endometrial sampling, 23 (10.2%) underwent fractional curettage and 21 (9.3%) underwent hysteroscopy with endometrial biopsy. Among them, 21 women were diagnosed with EH/EC, giving a prevalence of 9.2%. The demographic information is presented in Table 1. The average age was 46.6 ± 8.2 years, with the main age group of women being 41–50 years (58.8%). The average BMI was 23.4 ± 3.0 kg/m², with the majority of individuals (66.8%) being within the normal range of 18.5–24.9. Concerning medical comorbidities, 4.4% were diagnosed with diabetes mellitus and 12.8% with hypertension. A majority of women were multiparous (72.6%), whereas 18.6% were postmenopausal.

The Histopathological report is shown in Table 1. The findings revealed that the most common histopathological pattern was proliferative phase endometrium (58.9%) and followed by secretory phase endometrium (16.9%). Endometrial polyps were found in 9.7% of cases, while 5.7% had endometrial hyperplasia (with or without atypia). Endometrial carcinoma was identified in 3.5% of participants. Histological subtypes included endometrioid adenocarcinoma in 4 cases, serous carcinoma in 1 case, clear cell carcinoma in 1 case, and mixed cell adenocarcinoma in 2 cases.

Table 2 shows the univariate analysis of risk factors for EH/EC. After using univariable logistic regression with significance defined at $p < 0.1$ for crude odds ratio calculation, women aged over 60 (crude OR 20.00, 95% CI 5.62, 71.15, $p < 0.001$), postmenopausal status (crude OR 7.78, 95% CI 3.02, 20.05, $p < 0.001$). DM (crude OR 4.71, 95% CI 1.12, 19.82, $p = 0.034$) and HT (crude OR 3.17, 95% CI 1.12, 8.97, $p = 0.030$) showed significant increased risk of EH/EC. Other variables including BMI subgroup, nationality, parity, tamoxifen use, smoking, and family history of breast or colorectal cancer were not significantly associated with EH/EC.

Table 1. Baseline characteristic of participants (n = 226).

Baseline characteristic	n (%)
Age (years), mean ± SD	46.61 ± 8.18
- ≤ 40	41 (18.2)
- 41-50	133 (58.8)
- 51-60	40 (17.7)
- > 60	12 (5.3)
BMI (kg/m2), mean ± SD	23.38 ± 3.01
- < 18.5	9 (4.0)
- 18.5-24.9	151 (66.8)
- 25-29.9	66 (29.2)
Nationality	
- Thai	207 (91.6)
- Non-Thai	19 (8.4)
Underlying disease	
- Diabetes mellitus	10 (4.4)
- Hypertension	29 (12.8)
Parity	
- Nulliparity	62 (27.4)
- Multiparity	164 (72.6)
Menopausal status	
- Premenopause	184 (81.4)
- Postmenopause	42 (18.6)
Tamoxifen used	5 (2.2)
Smoking	2 (0.9)
History of breast cancer in family	4 (1.8)
History of colorectal cancer in family	2 (0.9)
Histopathology result	
- Proliferative phase endometrium	133 (58.9)
- Secretory phase endometrium	38 (16.9)
- Atrophy endometrium	12 (5.3)
- Endometrial polyp	22 (9.7)
- Endometrial hyperplasia without atypia	12 (5.3)
- Endometrial hyperplasia with atypia	1 (0.4)
- Endometrial cancer	8 (3.5)

BMI: body mass index, SD: standard division
Histopathology results from endometrial sampling or fractional curettage or hysteroscopy with endometrial biopsy.

Table 2. Factors associated with endometrial hyperplasia and endometrial carcinoma.

Variables	Endometrial hyperplasia and Endometrial carcinoma		Crude OR (95% CI)	p value
	No n = 205	Yes n = 21		
Age (years)				
- ≤ 60	200 (97.6)	14 (66.7)	Ref	-
- > 60	5 (2.4)	7 (33.3)	20.00 (5.62,71.15)	< 0.001*
BMI (kg/m^2)				
- < 18.5	9 (4.3)	-	-	0.999
- 18.5-24.9	135 (65.9)	16 (76.2)	Ref	-
- 25-29.9	61 (29.8)	5 (23.8)	0.69 (0.24,1.97)	0.491
Nationality				
- Thai	186 (90.7)	21 (100.0)	-	0.998
- Non-Thai	19 (9.3)	-	Ref	-
Diabetes mellitus	7 (3.4)	3 (14.3)	4.71 (1.12,19.82)	0.034*
Hypertension	23 (11.2)	6 (28.6)	3.17 (1.12,8.97)	0.030*
Parity				
- Nulliparity	57 (27.8)	5 (23.8)	0.81 (0.28,2.32)	0.696
- Multiparity	148 (72.2)	16 (76.2)	Ref	-
Menopausal status				
- Premenopause	175 (85.4)	9 (42.9)	Ref	-
- Postmenopause	30 (14.6)	12 (57.1)	7.78 (3.02,20.05)	< 0.001*
Tamoxifen used	5 (2.4)	-	-	0.999
Smoking	2 (1.0)	-	-	0.999
History of breast cancer in family	4 (2.0)	-	-	0.999
History of colorectal cancer in family	2 (1.0)	-	-	0.999

Values are presented as number (%). BMI: body mass index, OR: odds ratio, CI: confidence interval
* significant at p < 0.05 using univariable logistic regression for crude odds ratio calculation.

Table 3 presents the outcomes of the multivariate logistic regression analysis. The current analysis identified that age above 60 years (aOR 12.27, 95% CI 1.93, 78.20, p = 0.008) and menopausal state (aOR 9.39, 95% CI 1.56, 56.71, p = 0.015) were statistically significant independent predictors of the disease. The significant relationships seen for diabetes and hypertension in the univariable analysis disappeared after controlling for age and menopausal state.

Table 3. Multivariate logistic regression of factors associated with endometrial hyperplasia and endometrial Carcinoma.

Variables	Endometrial hyperplasia and Endometrial Carcinoma		Crude OR (95% CI)	Adjusted OR (95% CI)	p value
	No n = 205	Yes n = 21			
Age (years)					
- ≤ 60	200 (97.6)	14 (66.7)	Ref	Ref	-
- > 60	5 (2.4)	7 (33.3)	20.00 (5.62,71.15)	12.27 (1.93,78.20)	0.008*
Diabetes mellitus	7 (3.4)	3 (14.3)	4.71 (1.12,19.82)	1.30 (0.16,10.89)	0.810
Hypertension	23 (11.2)	6 (28.6)	3.17 (1.12,8.97)	0.55 (0.07,4.34)	0.571
Menopausal status					
- Premenopause	175 (85.4)	9 (42.9)	Ref	Ref	-
- Postmenopause	30 (14.6)	12 (57.1)	7.78 (3.02,20.05)	9.39 (1.56,56.71)	0.015*

Values are presented as number (%).
OR: odds ratio, CI: confidence interval
* significant at p < 0.05, significant after multivariate adjustment using multivariable logistic regression for adjusted odds ratio calculation.

Discussion

The prevalence of EH/EC among women with AUB and BMI less than 30 kg/m² in the present study was 9.2%. This prevalence was higher than that reported by Sattanakho et al[9], who found a prevalence of 4%, and by Jha et al[12], who reported a prevalence of 4.7% in women with AUB and BMI less than 30 kg/m². The lower prevalence observed in these 2 studies may be explained by both focused on low-risk, premenopausal women. In contrast, the present study included both premenopausal and postmenopausal women and incorporated additional risk factors, such as nulliparity and tamoxifen use, which may have contributed to the higher observed prevalence.

Age above 60 years and postmenopausal status were the most predictive factors for EH/EC in the present study, accounting for 58.3% of women aged more than 60 years and 28.0% of postmenopausal women. The findings aligned with the disease's epidemiology, which typically affects women aged 60–70 years[17]. The findings also aligned with the 2020 study by Clarke et al[13], which revealed a 17.7% risk of EH/EC in women over 60 years who presented with postmenopausal bleeding (risk 17.7%, 95% CI 13.0, 22.3%, p < 0.001). Similarly, in a study by Suwanwanich in 2019[11], postmenopausal status was also identified as a strong risk factor for EH/EC, with 68.52% of all postmenopausal women affected (RR 4.74, 95% CI 2.5, 9, p < 0.001). Consistent with the study by Sompratthana et al in 2024[18], which reported that aged over 60 years were independently associated with concurrent endometrial cancer, with an adjusted odds ratio of 4.37 (95% CI 1.04, 18.29, p = 0.04) among patients with endometrioid intraepithelial neoplasia (EIN). Although the study population differed from the present study, their results reinforced the importance of older age as a strong risk factor for endometrial cancer.

Diabetes and hypertension were significant in univariate analysis but lost significance after multivariate analysis. The lack of significance may be explained by the exclusion of women with a BMI more

than 30 kg/m² in the present study, which reduced the number of participants with diabetes and hypertension and limited their statistical impact. Compare with other studies such as Suwanwanich in 2019[11], which reported a relative risk of diabetes mellitus (DM) of 3.65 (95% CI 1.8, 7.3, p < 0.001) and HT of 3.33 (95% CI 1.7, 6.4, p < 0.001), and the study of Giannella et al in 2019[14], which highlighted DM as a strong risk factor for EH/EC with an adjusted odds ratio of 9.71 (95% CI 1.63, 57.81, p = 0.012), which may be because neither of the two studies controlled for obesity. By contrast, the study of Wise et al in 2016[15] reported diabetes and hypertension showed no effect, while BMI was a dominant predictor for EH/EC, possibly due to small subgroup numbers. As a result, some variables may have appeared nonsignificant; for example, young healthy women were not usually screened for diabetes.

Nulliparity was not significantly associated with EH/EC in this present study (OR 0.81, 95% CI 0.28, 2.32, p = 0.696). A possible explanation was participants in this group had a mean age of 44.0 ± 7.3 years, and most were premenopausal women, which likely reduced the risk of EH/EC in this subgroup. Similarly, the study by Giannella et al[14] also reported that nulliparity was not significantly associated with EH/EC (OR 3.00; 95% CI 0.93, 9.67; p = 0.065). But contrast with Suwanwanich[14], which showed a relative risk of nulliparous 7.44 (95% CI 3.6, 15.6, p < 0.001). Because of 1. the exclusion of women with BMI > 30 kg/m² in our study removed a critical synergistic factor. Obesity drives peripheral aromatization of androgens to estrogens; without this substrate, nulliparity alone may be insufficient to generate the threshold of unopposed estrogen required for neoplastic transformation. 2. Our study was predominantly premenopausal with a mean age of 44 years. Unlike older studies where nulliparity reflects a lifetime of cumulative exposure, our participants retained cyclic progesterone protection (luteal phase) during regular menstrual cycles. This suggested that in non-obese, premenopausal women, nulliparity was not an independent predictor of EH/EC, whereas in older or obese populations (as likely seen in Suwanwanich), it served as a proxy for chronic anovulation and long-term estrogen exposure.

The analysis of tamoxifen usage in the current investigation was precluded by the limited number of cases, aligning with Suwanwanich in 2019[11] (RR 2.08, 95% CI 0.6, 7.2, p = 0.221), where the small cohort of patients administered tamoxifen restricted the capacity to formulate definitive findings. However, the current study differs from Chen et al[16], who concentrated on women with breast cancer undergoing tamoxifen treatment in comparison to non-users. The logistic regression analysis, conducted with a sufficiently enough sample size, established a significant correlation between tamoxifen usage and the incidence of endometrial cancer (OR 2.94; 95% CI 2.13, 4.06; p < 0.001). In contrast, a study of Suwanwanich in 2024[19], which assessed the risk of EH/EC in premenopausal women with AUB, identified tamoxifen (95% CI 1.33, 165.76; p=0.041) as significant predictors. This difference may be explained by variations in study population and methodology, as that study included obese women and incorporated endometrial thickness > 10 mm into the risk assessment model, thereby increasing the likelihood of detecting such associations.

The strength was that the present study focused specifically on AUB in patients with a BMI of less than 30 kg/m². All participants met the strict inclusion criteria, and diagnoses were confirmed by histopathological findings

This study was conducted in a single center, which may limit the generalizability of the findings to other populations. The retrospective design limited the analysis to variables available in medical records, and some relevant risk factors could not be fully assessed. The sample size was relatively small for evaluating uncommon exposures such as tamoxifen used, smoking, or family history of breast or colorectal cancer, thereby limiting the statistical power to detect associations. Furthermore, direct measures of body fat composition and distribution were not available, which may have led to underestimation of the true

effect of adiposity on endometrial pathology.

The study demonstrated that even among women with BMI less than 30 kg/m², the prevalence of EH/EC was considerable (9.2%). Age above 60 years and postmenopausal bleeding were independent predictors. These findings suggest that clinicians should prioritize early endometrial assessment in older and postmenopausal women presenting with AUB, regardless of BMI. Incorporating age and menopausal status into triage algorithms may improve timely diagnosis and patient outcomes.

Conclusion

The prevalence of EH/EC among women with AUB and BMI less than 30 kg/m² was 9.2%. Postmenopause was an important factor for the disease. The risk increased significantly with age, especially after being 60 years old. These findings suggest that early detection strategies should be considered, particularly in older and postmenopausal women presenting with AUB.

Potential conflicts of interest

The authors declare no conflicts of interest.

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