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EDITORIAL

Intriguing Review and Topics in Second Issue of Thai Journal of Obstetrics and Gynaecology 2025

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 2025 contains many interesting articles. The special article is "Sodium bicarbonate vaginal suppositories for cytolytic vaginitis treatment". The contents included the definition of cytolytic vaginitis, diagnosis and treatment[1].

This issue also contains eight original articles. Sabyeying et al performed a retrospective cohort study to determine the age cut-off for endometrial biopsy in women with abnormal uterine bleeding to detect endometrial intraepithelial neoplasia and endometrial carcinoma in patients with abnormal uterine bleeding. They found that age group ≥ 45 years showed a moderate impact negative likelihood ratio compared to other age groups, with a sensitivity of 94.17% and a specificity of 41.06%. The risk factors including age ≥ 45 years, nulliparity, menopause status, diabetes mellitus, polycystic ovarian syndrome, endometrial thickness of 4 and 7 mm or thicker were significantly associated with endometrial intraepithelial neoplasia and endometrial carcinoma[2]. Warintaksa et al performed a prospective cohort study to compare ductus venosus (DV) shunting between uncomplicated pregnancy and gestational diabetes mellitus. The result showed that there was no significant change of DV shunting between uncomplicated pregnancy and gestational diabetes mellitus[3]. Charoenwong et al performed a double-blind, randomized controlled trial to compare the pre- and postoperative anxiety score by State-Trait Anxiety Inventory and visual analogue scale of anxiety of the patients who received preoperative oral diazepam with those who received a placebo during loop electrosurgical excision procedure (LEEP). They found that preoperative oral diazepam 10 mg administered one hour before operation did not decrease the pre- and postoperative anxiety or pain levels in LEEP[4]. Suwannapab et al performed a randomized controlled trial evaluate the effectiveness of 10% lidocaine spray for reducing postpartum perineal wound pain. The result revealed perineal wound pain at 24 and 48 hours in the lidocaine spray group was significantly lower than the control group. Pain intensity in the lidocaine spray group was also significantly lower than the control group[5]. Hengphrathani et al performed a double-blind, randomized controlled trial to evaluate the efficacy of oral vitamin D supplementation in improving vulvovaginal atrophy in postmenopausal women over a 12-week period. They found those administered with vitamin D exhibited statistically significant enhancements in vaginal health index[6]. Chuaysatit et al performed a cross-sectional study to evaluate patients' satisfaction with the preoperative informed consent process in elective gynecological surgery. The result showed high patient satisfaction was achieved when communication and patient participation were prioritized[7]. Chattrakoonphong et al performed an analytic cross-sectional study to compare the rate of gestational age (GA) re-dating after determination of GA using ultrasonography (US) in clinically reliable and clinically non-reliable pregnant women during the first trimester.

The result showed nearly half of the pregnant women needed GA re-dating when undergoing US in the first trimester of pregnancy. The rate of GA re-dating was similar in the clinically reliable and clinically non-reliable groups without any hint of clinical factor influence[8]. Srimaneesiri et al performed a randomized controlled trial evaluate the effects of combining vitamin C with iron supplementation on Hb and Hct levels among pregnant women at high risk of anemia. The result showed there were no significant differences in Hb and Hct levels between the two groups, both initially and 2 months after the intervention. Thus, vitamin C was not essential with iron supplements to improve Hb and Hct levels in pregnant women at risk of anemia[9].

Finally, we are pleased to announce that the Thai Journal of Obstetrics and Gynecology (TJOG) has received the results of the 5th round of the quality assessment of academic journals in the Thai Journal Citation Index (TCI) database. TJOG has been classified as a Tier 1 journal in the TCI database (2025-2029). We would like to thank the RTCOG Executive Committee, former Editors-in-Chief, editorial board and staff, reviewers, members of the RTCOG, and all researchers for their support and assistance to TJOG.

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SPECIAL ARTICLE

Sodium Bicarbonate Vaginal Suppositories for Cytolytic Vaginitis Treatment

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ABSTRACT

Cytolytic vaginitis (CV) is a form of vaginal dysbiosis resulting from an overgrowth of *Lactobacilli*, which are the primary protective bacteria in the vagina. The symptoms closely resemble those of fungal vaginitis, including abnormal vaginal discharge, itching, dysuria, and dyspareunia. There is no accurate diagnostic method, but bed-side diagnosis requires microscopic examination and pH testing. The Royal Thai College of Obstetricians and Gynaecologists outlines the following diagnostic guidelines: vaginal acidity (pH < 4.5), absence of vaginal fungal hyphae, and a higher number of white blood cells than squamous epithelial cells. In contrast, cytolytic vaginosis is defined by a high concentration of *Lactobacilli* with predominant epithelial cells with cytolysis. Patients with either condition often experience similar symptoms and may have a history of various unsuccessful treatments. The recommended treatment includes vaginal douching with a sodium carbonate solution or the use of sodium bicarbonate suppositories. The vaginal douching can be difficult to follow, particularly for Thai women. The Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, has used 300 mg sodium bicarbonate tablets (Sodamint®) as vaginal suppositories to treat this condition. This article aims to demonstrate our treatment experience, potentially contributing to the development of further knowledge and research.

Keywords: cytolytic vaginitis, cytolytic vaginosis, sodium bicarbonate, treatment, suppository.

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Introduction

Cytolytic vaginosis, first described in 1961, affects approximately 5% of women with abnormal vaginal discharge. Diagnosing this condition can be a challenge as its symptoms resemble those of fungal vaginitis, and the microscopic features appear close to normal. The risk factors include pregnancy and being under 40 years of age. It is less common in women who engage in frequent sexual intercourse. Common symptoms include vaginal itching, increased vaginal discharge, dysuria, and dyspareunia. Some individuals experience symptoms that vary with their menstrual cycle, worsening during ovulation and improving before menstruation. Microscopically, a large number of *Lactobacilli* are typically observed, with white blood cells rarely present, though squamous epithelial cells can be found with cytolytic pictures. Some experts recommend performing fungal cultures to differentiate between conditions, though both can coexist[1].

Cytolytic vaginosis, lactobacillosis and leptothrix, all of which result from an increase in the number of *Lactobacilli*, have indistinguishably clear definition. Typically, *Lactobacilli* are beneficial bacteria that protect the vagina in women of all ethnicities. Studies from various countries published since 2017 have identified *L. crispatus* as the most common Lactobacillus species. In cases of cytolytic vaginosis, it was observed that there is an increased production of acid in the vagina, and women with this condition exhibit lower diversity of *Lactobacilli* compared to normal[2]. These three conditions overlap, thus some experts suggest that cytolytic vaginosis is characterized by an increase in number of *Lactobacilli* and cytolysis. In contrast, lactobacillosis and leptothrix do not involve cytolysis. Leptothrix has a distinctive microscopic appearance, which is long and coiled, and believed to be a type of *Lactobacilli*[3].

Diagnosis

Patients with lactobacillosis and leptothrix, are often asymptomatic. Although antibiotic treatment is sometimes recommended, its benefits remain unclear. Leptothrix is diagnosed by identifying long, non-branching filamentous *Lactobacilli* (> 60µm)[3]. In a study by Vieira-Baptista, of 3,620 slides of vaginal swab, 102 (102/3620, 2.8%) met the criteria for leptothrix. Among the symptomatic group, 45 individuals (45/1847, 2.4%) had leptothrix. Of them, only 12 cases are potentially linked to the symptoms. The most common symptoms, listed in order, were vaginal burning and itching, abnormal vaginal discharge, menstrual symptoms, and dyspareunia. The average age of patients was 38.8 ± 10.65 years. The only associated risk factor identified was having human immunodeficiency virus (HIV). Leptothrix was also found in conjunction with fungal vaginitis by nearly doubling the risk (odds ratio (OR) 1.90, 1.16-3.10-3.10)[4]. However, this study could not clearly establish the relationship between the disease and the abovementioned symptoms.

The Royal Thai College of Obstetricians and Gynaecologists has introduced a management guideline for women presenting with abnormal vaginal discharge[5]. This guideline suggests a diagnostic method based on pH levels and the ratio of white blood cell to squamous epithelial cells (Fig. 1). Unlike the diagnostic method for cytolytic vaginosis, treatment in this guideline is initiated when a woman has abnormal vaginal discharge, a higher number of white blood cells than squamous epithelial cells, and a pH level below 4.5. This condition is referred to as cytolytic vaginitis due to elevated white blood cell count. The rationale is that the disease progression resembles that of fungal vaginitis: initially, the number of squamous epithelial cells is higher, but as inflammation and cell lysis increase, more white blood cells migrate into the vagina, resulting in a higher white blood cell count[6].

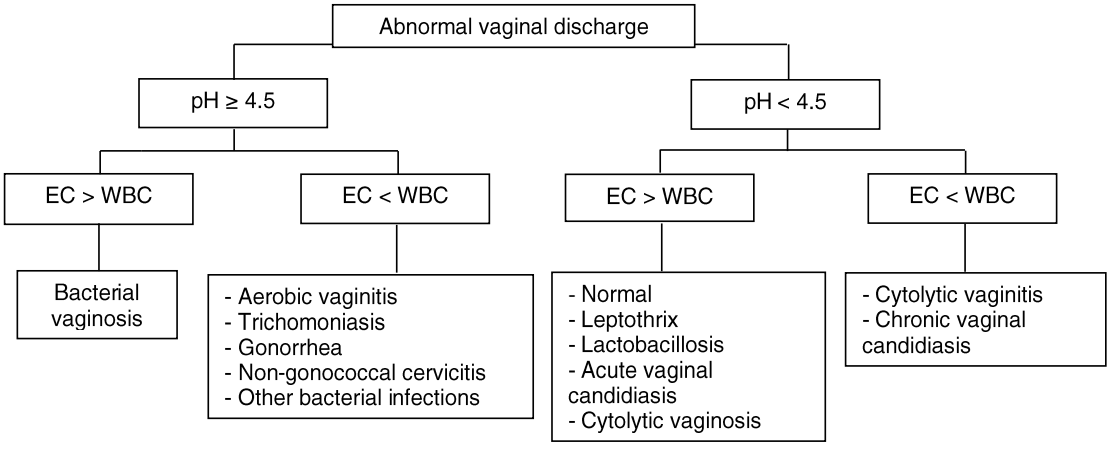

Fig. 1. Approach to abnormal vaginal discharge using vaginal pH and the ratio of epithelial cells to white blood cells.[5]

EC: epithelial cells, WBC: white blood cell

The prevalence of cytolytic vaginosis, lactobacillosis and leptothrix in Thai women has not been reported. One explanation is that the wet preparation of cytolytic vaginosis, lactobacillosis and leptothrix normally shows predominate squamous epithelial cells and share high similarity with the normal one. In contrast, microscopic finding of cytolytic vaginitis strikingly differs from that of normal vaginal discharge. Based on the unpublished data of the Siriraj Female STI Clinic, 49/186 (26.3%) of women presenting with abnormal vaginal discharge had vaginal pH < 4.5 and white blood cells ≥ 30/hpf. Of them, 20 had detected pseudohyphae in wet preparation. Therefore, 29/186 (15.6%) met the diagnostic criteria of cytolytic vaginitis. However, only a few of them agreed to try the novel treatment of Sodamint® and the treatment outcomes were shown in Table 1.

Treatment

Research on cytolytic vaginosis is limited. One study, conducted in Turkish women who underwent cervical Pap smears during 2015-2018, included 3,000 specimens. Those with ruptured squamous epithelium with bare nuclei; an increased number of *Lactobacilli*; few or no leukocytes; and no other significant bacteria were selected. Only patients with abnormal vaginal discharge and a pH ≤ 4.5 were selected, resulting in 53 patients (1.7%) being treated. The treatment involved mixing 1 tablespoon of sodium bicarbonate mixed with 4 liters of warm water, with patients sitting in the bathtub every other day for 10 days. All patients showed symptom improvement, with 43 patients (81%) improving at the start of treatment, and 10 (19%) showing improvement upon completing the treatment[7].

The treatment guidelines align with those for other types of vaginal dysbiosis, recommending treatment only when symptoms are present[3, 8]. The primary treatment method of cytolytic vaginosis and cytolytic vaginitis involves using a sodium carbonate solution for vaginal douching or sitting in a bath. This is typically recommended every morning for two weeks; however, some patients may require longer treatment or need to repeat the process whenever symptoms occur[3]. Other recommendations include avoiding tampons or vaginal cups; using antibiotics and fungicides only when necessary; exercising caution

when using probiotics; and avoiding excessive washing of the external genitalia[2]. The use of antibiotics is controversial, though clindamycin cream (2%) inserted into the vagina daily for 5 days or amoxicillin 500 mg taken orally three times a day for 7 days has been suggested[2]. The insertion of lactic acid products into the vagina is contraindicated, as it may increase the number of *Lactobacilli* and alter vaginal pH[9].

The use of vaginal suppositories to balance the vaginal environment is common, although its popularity varies across cultures. A study among female personnel working at Siriraj Hospital found that only 4.6% engaged in vaginal douching[10]. In contrast, various products are advertised in other countries as beneficial for promoting vaginal health. One study compared the effects of three products used for vaginal douching: water, sodium chloride, vinegar, and sodium benzoate (pH 3.0); citric acid, edetate disodium, water, sodium benzoate, sodium lauryl sulfate, trisodium phosphate, and povidone-iodine 0.3% (pH 3.5); and sodium bicarbonate and water (pH 9). The study found all three products could reduce *E.coli*, weaken the vaginal mucosa, and decrease the inflammatory effects of *Lactobacilli*. However, only sodium bicarbonate is effective at reducing the number of all types of *Lactobacilli* species, including *L. iners*, *L. crispatus, L. gasseri,* and *L. jensenii*[11]. This makes sodium bicarbonate a potential option for treating this condition.

In Thailand, sodium bicarbonate is available in two forms: as a solution and as an oral tablet (Sodamint®). It acts by reducing acidity in the bloodstream and stomach and alkalinizing the urine. This medication is inexpensive and readily available at all levels of medical facilities. The Royal Thai College of Obstetricians and Gynaecologists recommends treating abnormal vaginal discharge using sodium carbonate solution mixed with 1.5 liters of water for vaginal douching[8]. However, this method can be challenging for patients to perform by themselves. Additionally, based on our experience in caring for women with abnormal vaginal discharge, we found that many Thai women are reluctant or fearful of using such treatment methods. Since The Thai treatment guidelines also recommend the use of sodium bicarbonate tablet (Sodamint® 300 mg) as a vaginal suppository once or twice daily for 10-14 days, we have some experience of this treatment choice, and the series of patients is summarized in Table 1.

Table 1. Case series of women with cytolytic vaginitis at the Siriraj Female STD Clinic (n = 12).

Cases	Age (y)	BMI (kg/m²)	No. of child (ren)	Contraceptive methods	Last Pap result	Previous diagnosis	Polymerase chain reaction results						Cure
							NG	CT	TV	MG	MH	UU	UP	
1	21	20.2	0	Condom	NILM, Candida	-	neg	neg	neg	neg	pos	neg	pos	Yes
2	24	24.8	1	No	NILM	Bacterial vaginosis	-	-	-	-	-	-	-	Yes
3	29	21.3	1	Condom	NILM	Aerobic vaginitis	neg	pos	-	-	-	-	-	Yes
4	51	18.4	2	No	NILM	Bacterial vaginosis	neg	neg	-	-	-	-	-	Yes
5	29	26.0	0	Condom	NILM	Aerobic vaginitis	neg	neg	-	-	-	-	-	Yes
6	37	28.8	1	Pills	NILM, Candida	-	pos	neg	-	-	-	-	-	Yes
7	40	16.9	2	Pills	NILM	-	neg	neg	-	-	-	-	-	Yes
8	33	18.8	0	No	NILM	-	-	-	-	-	-	-	-	Yes
9	46	19.1	3	Sterilisation	NILM	Vaginal candidiasis	neg	neg	neg	neg	neg	neg	neg	No
10	42	29.6	1	Sterilisation	NILM	Aerobic vaginitis	neg	neg	neg	neg	neg	neg	neg	No
11	27	19.6	1	DMPA/Implant	ASCUS	Aerobic vaginitis	neg	pos	neg	pos	neg	pos	neg	No
12	23	26.1	1	No	NILM	Aerobic vaginitis	neg	pos	neg	neg	pos	neg	pos	No

BMI: body mass index, NILM: negative intraepithelial lesions or malignancy, ASCUS: atypical squamous cell of unknown significance, NG: N. gonorrhoeae, CT: *C. trachomatis*, TV: *T.vaginalis*, MG: *M. genitalium*, MH: *M. hominis*, UU: *U.urealyticum*, UP: *U.parvum*, DMPA: depot medroxyprogesterone acetate
Source: Unit of Infectious Diseases, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University

Initially, we started with Sodamint® vaginal suppositories administered in the morning and evening. However, two out of four patients reported discomfort, including burning, itching, and vaginal irritation. Since then, we adjusted the dosage to once daily for 10-14 days, followed by a two-week follow-up appointment for all patients. Out of 15 patients diagnosed with cytolytic vaginitis, 12 returned for the follow-up. A clinical cure was observed in 8 out of 12 patients (66.7%). Those who did not achieve a clinical cure were more likely to have child (ren), practice unprotected intercourse, and have a history of vaginal dysbiosis. No co-infections with vaginal candidiasis or trichomoniasis were found. Additionally, none of the patients reported severe adverse effects that required premature discontinuation of Sodamint®. After treatment, two out of 12 patients (16.7%) experienced a recurrence of symptoms and managed it by using the suppositories on an as-needed basis.

Other forms of sodium carbonate have been used to treat vaginitis caused by various factors. For instance, sodium bicarbonate gel has been used to treat fungal vaginitis. Studies have shown that this gel can reduce the growth of *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. albicans*, with an optimal concentration of 5%. In vitro studies indicate that sodium bicarbonate can be used with Hela cells, which are a good model for vaginal epithelial cells, as it does not cause irritation[12]. Another study showed that using 5% sodium bicarbonate solution as a sitz bath once daily for 14 days, compared to a sitz bath with nystatin 500,000 units for the same duration, found no significant difference in the rate of symptom resolution or microscopic diagnosis. However, the group using nystatin experienced faster symptom relief. It is believed that reducing vaginal acidity can help limit fungal growth[13].

In general, various types of drugs can be administered vaginally, including hormonal medications, antibiotics, and antifungal agents. The benefits of this route of administration include localized action, no interference with gastrointestinal absorption or interactions with orally absorbed drugs, and ease of use[14]. Additionally, vaginal secretions from the fallopian tubes, uterus, Bartholin's gland, and Skene's gland enhance drug solubility[15]. Vaginal drug delivery also tends to have fewer side effects, reducing the risk of those associated with oral medications. This may help improve patient adherence[14]. In line with our case series, some studies showed that sodium bicarbonate in gel form causes irritation in the vulvovaginal area[12].

Conclusion

Cytolytic vaginosis or cytolytic vaginitis is a form of vaginal dysbiosis caused by an overgrowth of *Lactobacilli*. Treatment involves adjusting the *Lactobacilli* levels by reducing vaginal acidity; addressing risk factors that may contribute to the imbalance; and promoting overall vaginal health such as avoiding excessive genital cleansing, managing stress and correcting nutrient deficiencies. While sodium bicarbonate solution is readily available, it may be less suitable for use among Thai women. Sodium bicarbonate vaginal suppository offers an affordable, easily accessible, and convenient treatment option. Nonetheless, further research with a larger study population size and further prospective studies are needed.

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Age-associated with Endometrial Intraepithelial Neoplasia and Endometrial Carcinoma in Patients with Abnormal Uterine Bleeding

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ABSTRACT

Objectives: To determine the age cut-off for endometrial biopsy in women with abnormal uterine bleeding to detect endometrial intraepithelial neoplasia and endometrial carcinoma in patients with abnormal uterine bleeding.

Materials and Methods: A total of 1,384 women presenting with abnormal uterine bleeding underwent endometrial biopsy at Maharat Nakhon Ratchasima Hospital between July 1, 2021, and June 30, 2023. This retrospective cohort study collected age and other risk factors of endometrial intraepithelial neoplasia and endometrial carcinoma, then calculated sensitivity, specificity, negative likelihood ratio, area under the curve (AUC) of each age cut-off and conducted multivariable logistic regression.

Results: The age group ≥ 45 years showed a moderate impact negative likelihood ratio (0.14, 95% confidence interval 0.07 - 0.31) and higher AUC (0.91) compared to other age groups, with a sensitivity of 94.17% and a specificity of 41.06%. The risk factors including age ≥ 45 years, nulliparity, menopause status, diabetes mellitus, polycystic ovarian syndrome, endometrial thickness of 4 and 7 mm or thicker were significantly associated with endometrial intraepithelial neoplasia and endometrial carcinoma.

Conclusion: Consider endometrial biopsy for screening of endometrial intraepithelial neoplasia and endometrial carcinoma in women aged 45 or older with abnormal uterine bleeding or those under 45 with risk factors such as nulliparity, diabetes mellitus, menopausal status, polycystic ovarian syndrome, and endometrial thickness of 4 and 7 mm or thicker.

Keywords: age, endometrial intraepithelial neoplasia, endometrial cancer, abnormal uterine bleeding, endometrial biopsy

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อายุที่สัมพันธ์กับภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยที่มีเลือดออกผิดปกติจากโพรงมดลูก

พิชญ์สินี สบายยิ่ง, ฐิตินันท์ สมุทรไชยกิจ, ดวงพร รัตนลาภไพบูลย์, ชญานิษฐ์ เดชวงศ์ญา

บทคัดย่อ

วัตถุประสงค์: *เพื่อกำหนดจุดตัดอายุที่เหมาะสมสำหรับการดูดชิ้นเนื้อเยื่อบุโพรงมดลูก (endometrial biopsy) ในผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูก เพื่อคัดกรองภาวะเยื่อบุโพรงมดลูกหนาผิดปกติ และมะเร็งเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังในผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูกและได้รับการดูดชิ้นเนื้อเยื่อบุโพรงมดลูก (endometrial biopsy) จำนวน 1,384 คน ที่เข้ารับการรักษาในโรงพยาบาลมหาราชนครราชสีมา ตั้งแต่ 1 กรกฎาคม พ.ศ. 2564 ถึง วันที่ 30 มิถุนายน พ.ศ. 2566 โดยรวบรวมอายุและปัจจัยเสี่ยงในการเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติ และมะเร็งเยื่อบุโพรงมดลูกที่บันทึกในเวชระเบียน คำนวณหาความไว (sensitivity) ความจำเพาะ (specificity) ความน่าจะเป็นเมื่อแบบทดสอบเป็นลบ (negative likelihood ratio) และพื้นที่ใต้กราฟ (area under curve) ของแต่ละจุดตัดอายุ รวมถึงวิเคราะห์การถดถอยเชิงพหุ*

ผลการศึกษา: *ในกลุ่มอายุ 45 ปีขึ้นไป มีความน่าจะเป็นเมื่อแบบทดสอบเป็นลบ (negative likelihood ratio) อยู่ในระดับ moderate (0.14, 95% confidence interval 0.07 - 0.31) และมีพื้นที่ใต้กราฟ (area under curve) 0.91 ซึ่งสูงกว่ากลุ่มอายุอื่น ร่วมกับมีความไว (sensitivity) ร้อยละ 94.17 และความจำเพาะ (specificity) ร้อยละ 41.06 นอกจากนี้พบว่าปัจจัยที่สัมพันธ์การเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติและมะเร็งเยื่อบุโพรงมดลูกอย่างมีนัยสำคัญคือ อายุ 45 ปีขึ้นไป ไม่เคยมีบุตร ภาวะหมดระดู โรคเบาหวาน ภาวะถุงน้ำรังไข่หลายใบ ภาวะเยื่อบุโพรงมดลูกหนา 4 หรือ 7 มิลลิเมตรขึ้นไป*

สรุป: *พิจารณาใช้อายุ 45 ปี ขึ้นไป เป็นจุดตัดในการคัดกรองผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูก ด้วยการดูดชิ้นเนื้อในโพรงมดลูก และส่งตรวจทางพยาธิวิทยา เนื่องจากสัมพันธ์กับภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก หรือพิจารณาคัดกรองในผู้ป่วยหญิงที่อายุน้อยกว่า 45 ปี ที่มีปัจจัยเสี่ยงของการเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติและมะเร็งเยื่อบุโพรงมดลูก ได้แก่ ไม่เคยมีบุตร โรคเบาหวาน ภาวะหมดระดู ภาวะถุงน้ำรังไข่หลายใบ เยื่อบุโพรงมดลูกหนา 4 หรือ 7 มิลลิเมตรขึ้นไป*

คำสำคัญ: *อายุ, ภาวะเยื่อบุโพรงมดลูกหนาผิดปกติ, มะเร็งเยื่อบุโพรงมดลูก, เลือดออกผิดปกติจากโพรงมดลูก, การดูดชิ้นเนื้อเยื่อบุโพรงมดลูก*

Introduction

Endometrial cancer is a common gynecologic malignancy. In 2023, there were 66,200 new cases of endometrial cancer and 13,030 deaths in the United States, accounting for 2.1% of all endometrial cancer cases[1]. In Thailand, endometrial cancer ranks as the second most common gynecologic malignancy, following cervical cancer as the most prevalent[2].

Endometrial hyperplasia is a precancerous lesion of endometrial cancer[3] caused by prolonged exposure to unopposed estrogen. Risk factors of endometrial hyperplasia include late menopause, obesity, diabetes mellitus, unopposed estrogen, and the use of tamoxifen[4]. Endometrial hyperplasia and endometrial cancer often manifest as abnormal uterine bleeding, and these conditions can be detected early through histological examination.

The American College of Obstetricians and Gynecologists (ACOG) recommends considering endometrial biopsy for women experiencing abnormal uterine bleeding who are aged 45 or older, or for those under 45 with risk factors such as obesity, polycystic ovarian syndrome, unsuccessful treatment, and persistent abnormal uterine bleeding[5].

While the Society of Obstetricians and Gynaecologists of Canada suggests that endometrial biopsy be considered for women aged 40 and older, as well as for those under 40 who have risk factors for endometrial cancer, such as nulliparity, body mass index (BMI) over 30 kg/m^2, polycystic ovarian syndrome, diabetes mellitus, history of hereditary nonpolyposis colorectal cancer (HNPCC), failed medication, and significant intermenstrual bleeding[6].

The recommendation for endometrial biopsy from different countries may have been suggested at different ages, and currently, there is no standard screening for endometrial cancer. In this study, we aimed to determine the age cut-off for endometrial biopsy to detect endometrial intraepithelial neoplasia and endometrial cancer in women presenting with abnormal uterine bleeding at Maharat Nakorn Ratchasima Hospital, as well as other risk factors such as BMI, menopausal status, polycystic ovarian syndrome, diabetes mellitus, hypertension, tamoxifen use, and dyslipidemia.

Materials and Methods

A retrospective cohort study, authorized by the institutional review board of Maharat Nakhon Ratchasima, examined the data of patients who presented with abnormal uterine bleeding and underwent endometrial biopsy for histology between July 1, 2021, and June 30, 2023. The abnormal histology included endometrial intraepithelial neoplasia and endometrial carcinoma, while the remaining cases were categorized as the less-than endometrial intraepithelial neoplasia (EIN) group. Because endometrial hyperplasia without atypia can develop into endometrial cancer at a rate of 5% in 20 years[7], or it can regress spontaneously, we classify it as less-than EIN group.

The sample size was calculated using the model literature developed by Corbacioglu Esmer et al[8]. The study revealed a 67.5% sensitivity in detecting endometrial hyperplasia with atypia and endometrial cancer in individuals aged 45 years or older. Therefore, a statistical formula was employed to calculate the proportion for the infinite population. At least 85 patients in the endometrial intraepithelial neoplasia and endometrial cancer group were required. Our pilot study, conducted from July 2021 to June 2022, indicated that 54 out of 760 patients presenting with abnormal uterine bleeding were diagnosed with endometrial cancer, accounting for 7.1%. Therefore, a sample size of 1,196 patients presenting with abnormal uterine bleeding who will undergo endometrial biopsy was required.

Women with abnormal uterine bleeding who had undergone endometrial biopsy at the age of 30 years or older during the study period were included. Patients were excluded if there was incomplete data, inability to interpret histology through endometrial biopsy, pregnancy, coagulopathy, or use of anticoagulant drugs. We gathered data on age, BMI, diabetes mellitus, hypertension, dyslipidemia, menopausal status, hormonal contraception use,

tamoxifen use, polycystic ovarian syndrome, and endometrial thickness.

Data were analyzed by STATA version 17.0 to determine sensitivity, specificity, negative likelihood ratio, and area under the curve. Multivariable logistic regression analysis was utilized to calculate associated factors of EIN and endometrial cancer, providing an adjusted odds ratio. A p value of < 0.05 was considered significant.

Results

A total of 1,658 women presented with abnormal uterine bleeding underwent endometrial biopsy at Maharat Nakorn Ratchasima Hospital. One hundred seventy-two women were excluded due to incomplete data, and 102 were excluded due to challenges in histology interpretation. As a result, the study included 1,384 women, which comprised 1,236 cases of normal histology, 45 cases of hyperplasia without atypia, 15 cases of endometrial intraepithelial hyperplasia, and 88 cases of endometrial cancer.

The demographic data presented in Table 1 revealed significant differences in age, BMI, parity, endometrial thickness, hypertension, diabetes mellitus, dyslipidemia, and hormonal contraception use between the EIN and endometrial cancer groups compared to the less-than-EIN group. However, there were no significant differences in polycystic ovarian syndrome and tamoxifen use. Additionally, the mean age was 46 years in the less-than-EIN group and 61 years in the endometrial intraepithelial hyperplasia and endometrial carcinoma group.

Table 1. Demographic characteristics.

Characteristic	EIN and Endometrial CA (n = 103)	Less than EIN (n = 1,281)	p value
Age			< 0.001*
< 35 years	2 (1.94)	46 (3.59)	
35 - 39 years	2 (1.94)	161 (12.57)	
40 - 44 years	2 (1.94)	319 (24.90)	
45 - 49 years	11 (10.68)	373 (29.12)	
≥ 50 years	86 (83.50)	382 (29.82)	
BMI			< 0.001*
< 23	30 (29.1)	600 (46.8)	
23 - 27.49	34 (33.0)	385 (30.1)	
≥ 27.5	39 (37.9)	296 (23.1)	
Parity			< 0.001*
0	25 (24.3)	196 (15.3)	
1 - 2	40 (38.8)	831 (64.9)	
> 2	38 (36.9)	254 (19.8)	
Menopause status	79 (76.7)	238 (18.6)	< 0.001*
Hypertension	58 (56.3)	295 (23.0)	< 0.001*
Diabetes mellitus	40 (38.8)	143 (11.2)	< 0.001*
Dyslipidemia	39 (37.9)	169 (13.2)	< 0.001*
Hormonal use	1 (1.0)	131 (10.2)	0.002*
PCOS	3 (2.9)	16 (1.3)	0.163
Tamoxifen	2 (1.9)	15 (1.2)	0.494
Endometrial thickness			< 0.001*
< 4 mm	9 (8.7)	587 (45.8)	
4 - 6.9 mm	14 (13.6)	199 (15.5)	
≥ 7 mm	80 (77.7)	495 (38.7)	

Data are shown as n (%)
EIN: endometrial intraepithelial neoplasia, CA: cancer, BMI: body mass index, PCOS: polycystic ovary syndrome
*p < 0.05 was considered statistically significant

When using age as the cut-off, the prevalence of endometrial intraepithelial neoplasia and endometrial cancer was highest in age ≥ 50 years group, followed by the age ≥ 45 years group (Table 2). Furthermore, when analyzing the age group, we found the percentage of endometrial intraepithelial hyperplasia and endometrial carcinoma cases of each age group (Fig 1).

Table 2. The prevalence of cut-off age in endometrial carcinoma and endometrial intraepithelial neoplasia.

Cut-off age (years)	Number of Patients (n)	Number of Endometrial cancer and EIN	Prevalence
≥ 35	1,366	101	7.39%
≥ 40	1,173	99	8.44%
≥ 45	852	97	11.38%
≥ 50	468	86	18.38%

* The proportion of endometrial intraepithelial neoplasia and endometrial carcinoma to number of patients in each age group
EIN: endometrial intraepithelial neoplasia

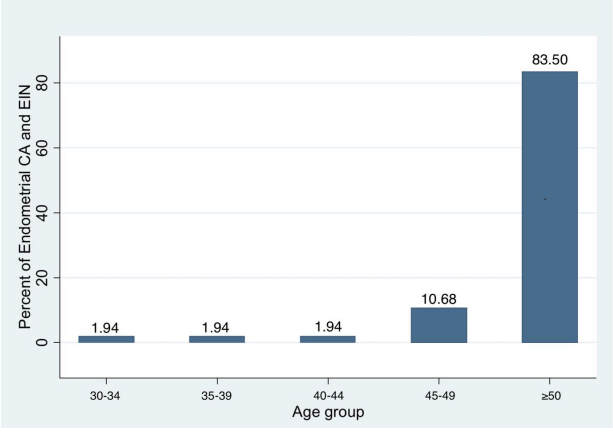

Fig. 1. The percentage of endometrial carcinoma and endometrial intraepithelial neoplasia in each age group.

However, the age ≥ 35 years had the highest sensitivity (98.1%, 95% confidence interval 0.93 - 0.99), followed by age ≥ 40 years, age ≥ 45 years, and age ≥ 50 years. In terms of specificity, we found that age ≥ 50 years had the highest specificity (70.18%, 95%CI 0.68 - 0.73), followed by age ≥ 45 years, age ≥ 40 years, and age ≥ 35 years. Concerning the negative likelihood ratio, we found that age ≥ 45 years had a moderate effect (0.14, 95%CI 0.07 - 0.31), while age ≥ 40 years and age ≥ 50 years had a small effect, and age ≥ 35 years had a minimal effect. Furthermore, our study revealed that age ≥ 50 years had the highest area under the curve (0.77), followed by age ≥ 45 years (0.68) (Table 3).

The research identified several factors associated with endometrial intraepithelial hyperplasia and endometrial carcinoma. By applying multiple logistic regression analysis to control for confounding variables, the study highlighted the following statistically significant factors, including age ≥ 45 years, nulliparity, menopause, diabetes, and endometrial thicknesses of 4-6.9 mm and 7 mm or more. Although polycystic ovarian syndrome initially appeared to be statistically insignificant, it was later determined to significantly increase the risk, after excluding other confounding variables (Table 4). Lastly, controlling other factors from this model, our study revealed that age ≥ 45 years had the highest area under the curve (0.9144).

Table 3. The sensitivity, specificity, negative likelihood ratio, and area under the receiver operating characteristic curve in endometrial carcinoma and endometrial intraepithelial neoplasia.

Cut-point age (years)	≥ 35	≥ 40	≥ 45	≥ 50
Negative LR	0.54	0.24	0.14	0.24
(95% CI)	(0.13-2.20)	(0.09 – 0.63)	(0.07 – 0.31)	(0.15 – 0.36)
Sensitivity	98.1%	96.12%	94.17%	83.50%
(95% CI)	(0.93-0.99)	(0.90 – 0.99)	(0.88 – 0.98)	(0.75 – 0.90)
Specificity	3.6%	16.16%	41.06%	70.18%
(95% CI)	(0.03-0.05)	(0.14 – 0.18)	(0.38 – 0.44)	(0.68 – 0.73)
AUC	0.51	0.56	0.68	0.77
(95% CI)	(0.49 - 0.52)	(0.54 – 0.58)	(0.65 – 0.70)	(0.73 – 0.81)

AUC: area under the receiver operating characteristic curve, EIN: endometrial intraepithelial neoplasia, LR: likelihood ratio, CI: confidence interval

Table 4. Logistic regression of factors associated with endometrial cancer and endometrial intraepithelial neoplasia.

Outcome	Odd ratio	p value	Adjusted odd ratio	p value
Age ≥ 45 years	11.26 (4.90, 25.88)	< 0.001	4.86 (1.74, 13.55)	0.003*
BMI				
< 23	1		1	
23-27.49	1.77 (1.06, 2.93)	0.028	1.59 (0.87, 2.89)	0.130
≥ 27.5	2.64 (1.60, 4.33)	< 0.001	1.72 (0.94, 3.16)	0.081
Parity				
0	2.65 (1.57, 4.47)	< 0.001	3.11 (1.65, 5.87)	< 0.001*
1-2	1		1	
> 2	3.11 (1.95, 4.95)	< 0.001	1.67 (0.97, 2.89)	0.065
Menopause status	14.43 (8.94, 23.27)	< 0.001	7.93 (4.42, 14.20)	< 0.001*
Hypertension	4.31 (2.86, 6.49)	< 0.001	1.28 (0.71, 2.29)	0.412
Diabetes mellitus	5.05 (3.28, 7.79)	< 0.001	2.35 (1.29, 4.31)	0.006*
Dyslipidemia	4.01 (2.61, 6.16)	< 0.001	1.26 (0.69, 2.32)	0.454
Hormonal use	0.09 (0.01, 0.62)	0.015	0.46 (0.06, 3.62)	0.463
PCOS	2.37 (0.68, 8.28)	0.176	10.43 (2.32, 46.84)	0.002*
Tamoxifen	1.67 (0.38, 7.41)	0.499	0.44 (0.09, 2.15)	0.311
Endometrial thickness				
< 4 mm	1		1	
4-6.9 mm	4.59 (1.96, 10.76)	< 0.001	4.96 (1.97, 12.47)	0.001*
≥ 7 mm	10.54 (2.24, 21.21)	< 0.001	10.25 (4.85, 21.66)	< 0.001*

*p < 0.05 was considered statistically significant

EIN: endometrial intraepithelial neoplasia, BMI: body mass index, PCOS: polycystic ovary syndrome

Discussion

Age is frequently a crucial factor in determining whether to conduct an endometrial biopsy in patients who are experiencing abnormal uterine bleeding when there are no other possible risk factors. Most institutions recommend starting an endometrial biopsy in women with abnormal uterine bleeding at the age of 35-45 to detect the abnormal endometrial pathology. ACOG 2019[5] and The Royal Thai College of Obstetricians and Gynaecologists (RTCOG) 2022[9] suggest starting at age 45, whereas other studies indicate screening at 35[10, 11] and 40[8]. As a result,

there is uncertainty about the cut-off age for endometrial biopsy screening to detect abnormal endometrial pathology.

This study found that the prevalence of endometrial intraepithelial neoplasia and endometrial cancer was higher when using cut-off ages of 40 and 45, ranging from 8.44% to 11.38%. This was increased compared to using cut-off ages of 35 and 40 years, which ranged from 7.54% to 8.44%. Notably, 11 women in the 45-49 age group were diagnosed with EIN or endometrial cancer, compared to two women each in the 30-34, 35-39 and 40-44 age groups.

When using age as a cut-off for deciding on endometrial biopsy in women who present with abnormal uterine bleeding without considering other risk factors, age ≥ 45 years had significantly higher specificity than age ≥ 40 years, while the sensitivities remained similar. Higher specificity reduces the chance of false positive rates in women without abnormal endometrial pathology, therefore avoiding unnecessary endometrial biopsy and increasing cost-effectiveness compared to the group with lower specificity.

Comparing age groups, those aged ≥ 35 years had the lowest specificity, while those aged ≥ 50 years had the lowest sensitivity. Therefore, utilizing ages ≥ 35 and ≥ 50 years as cut-offs is unsuitable. Setting the age cut-off at 35 years would result in more unnecessary endometrial biopsies, whereas setting it at age 50 years would lead to a higher false negative rate, missing EIN or endometrial cancer in many cases. Therefore, utilizing an age ≥ 45 years is the most appropriate cut-off for screening endometrial biopsy in women with abnormal uterine bleeding.

When considering the negative likelihood ratio, it was found that setting the age cutoff at ≥ 45 years has a moderate impact. This indicated that patients under the age of 45 presenting with abnormal uterine bleeding and having normal histopathological results were less likely to develop endometrial cancer or endometrial intraepithelial neoplasm compared to other cut-off points with minimal or small effects. In terms of the area under the curve (AUC), after adjusting for other potential confounding variables, it was found that the AUC for people aged ≥ 45 years was a good level and the highest (0.9144). Although not significantly different from other age cutoffs, it consistently performed well across all age cut-offs.

Among patients under the age of 45, there were four cases of endometrial cancer and two cases of endometrial intraepithelial neoplasm. Each individual had risk factors for developing endometrial intraepithelial neoplasm and endometrial cancer higher than those in the general population. For instance, the first endometrial cancer case had an abnormal papanicolaou smear result atypical glandular cells (AGC), the second case had morbid obesity (BMI 70 kg/m^2), diabetes mellitus at young age, and polycystic ovarian syndrome, the third case had obesity (BMI 34.63 kg/m^2), diabetes mellitus at young age, and nulliparity, and the fourth case had morbid obesity (BMI 39.13 kg/m^2) and diabetes mellitus at young age. In patients with endometrial intraepithelial neoplasm, one was obese (BMI 29.97 kg/m^2), nulliparous, and had polycystic ovarian syndrome, while the other was obese (BMI 30.4 kg/m^2) and also had polycystic ovarian syndrome. From this study, patients under the age of 45 with abnormal histopathology, such as endometrial intraepithelial neoplasm and endometrial cancer, had significantly higher risk factors compared to the general population.

This study selected an age cut-off of ≥ 45 years, which aligns with the RTCOG 2022[9] and ACOG 2019[5] recommendations for endometrial biopsy, disregarding other risk factors. This was consistent with a study by Iram[12], which used an age cutoff of ≥ 45 years with a sensitivity of 70%, specificity of 63%, and an AUC of 0.646. However, this differed from a study conducted by Corbacioglu Esmer[8], which utilized a cut-off of ≥ 40 years. This difference might be due to ethnic diversity since their study population was European, while this study focused on an Asian population. There might be hidden risk factors that contribute to the development of endometrial cancer or endometrial intraepithelial neoplasm in the

population, which were not mentioned in their studies. Apart from age, other significant risk factors for endometrial intraepithelial neoplasm and endometrial cancer include nulliparity, diabetes, and menopause, which increase the risk by 4.69, 2.33, and 8.23, respectively. These findings aligned with studies by Jayawickcrama[13], Zhao[14], Özdemir[15], and Suwanwanich[10]. For polycystic ovarian syndrome, after controlling for other confounding variables, it was found to significantly increase the risk by 10.34, similar to a study by Barry[16], which found a significant increase of 2.79.

When assessing endometrial thickness, the average endometrial thickness in the less-than-EIN group was found to be 7 mm, consistent with a study by Van Den Bosch[17], which indicated that the thickness of atrophic endometrium can reach up to 7 mm. For this reason, this study established cut-off points at 4 mm and 7 mm, showing that endometrial thickness ≥ 4 mm and ≥ 7 mm significantly increases the risk by 4.96 and 10.25, respectively. These results were consistent with a study by Thoprasert[18] and Suwanwanich's studies[19] which reported endometrial thickness cut-off points at ≥ 8 mm and ≥ 10 mm, respectively. Interestingly, the optimal endometrial thickness cut-off values should be studies further.

In the study, obesity was noted to significantly increase the risk of developing endometrial intraepithelial neoplasm and endometrial cancer by 1.77 and 2.64, but after controlling for confounding variables such as diabetes and others, it was not statistically significant. In terms of hypertension and dyslipidemia, they were not found to statistically significantly increase the risk, in contrast to previous studies[14, 19, 20], which may be due to these three conditions acting as confounding factors for diabetes. Regarding the use of hormonal contraceptives and tamoxifen, after accounting for confounding variables, there was no statistically significant association, which contrasted with previous studies[19, 21, 22], possibly due to the small size of the population in this study using these medications.

A strength of this study was the utilization of electronic medical records data, which allowed for the retrospective gathering of age and assessing the risk of endometrial cancer. On the other hand, the study was limited as it is based on data from a single institution with retrospective data. Furthermore, the reliability of data such as contraceptive and tamoxifen use may be limited.

The benefits of this study were that it provided insight into the appropriate age for performing endometrial biopsy to minimize the risk of false negatives, ensuring the diagnosis of EIN and endometrial carcinoma. Additionally, it advocated avoiding unnecessary tissue biopsy in younger and low-risk patients, thereby increasing the cost-effectiveness of endometrial biopsy in the future. Moreover, future studies should explore the predictive scores to enhance the accuracy of selecting candidates for endometrial biopsy in women who present with abnormal uterine bleeding.

Conclusion

The use of age ≥ 45 years as a cut-off for screening and conducting endometrial biopsy in women who present with abnormal uterine bleeding is recommended due to its high sensitivity, specificity, and favorable negative likelihood ratio. Even in cases where women are younger than 45 years but exhibit significant risk factors, including nulliparity, polycystic ovarian syndrome, diabetes mellitus, menopause, and an endometrial thickness of 4-7 mm or more, performing an endometrial biopsy is also advised.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Ductus Venosus Shunting in Pregnancies with Well-Controlled Gestational Diabetes Mellitus

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) is a common metabolic disorder in pregnancy, and it can be identified in 20% to 25% of Southeast Asian pregnancies. For GDM, fetal hypermetabolic rate due to hyperinsulinemia may cause an increase in hepatic blood flow from the umbilical venous (UV), leading to a decrease in ductus venosus (DV) shunting. The objective of this study was to compare DV shunting between uncomplicated pregnancy and gestational diabetes mellitus.

Materials and Methods: A prospective cohort study was performed on 76 women with uncomplicated singleton pregnancies and 36 women with GDM. Ductus venosus flow (DVF) and umbilical venous flow (UVF) were measured to assess the degree of DV shunting at 28-32 weeks of gestation. Pregnancy and neonatal outcomes were also collected and analyzed, including antenatal complications, gestational age at delivery, birth weight, Apgar score, neonatal intensive care unit (NICU) admission, ventilator support, and neonatal morbidity.

Results: The baseline characteristics of both groups were not significantly different, except for mean maternal age. There was no difference in the degree of DV shunting between the GDM and the control groups after adjustment for maternal age and gestational age, 41.34 % vs 40.18 %, respectively ($p = 0.70$). After multiple linear regression analysis, DVF, UVF, and DV shunting with an adjustment for maternal age and gestational age (GA) did not show a statistically significant difference. No relationships were found between the hemodynamic variables and perinatal outcomes.

Conclusion: This study suggested that good control of maternal GDM may prevent an increase in fetal hepatic blood flow, as indicated by no significant change of DV shunting and UVF.

Keywords: Doppler sonography, fetal circulation, fetal ultrasonography.

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การศึกษาเปรียบเทียบการเปลี่ยนแปลงการไหลของหลอดเลือดดำสายสะดือเข้าสู่หลอดเลือด Ductus venosus ทารกในครรภ์ของมารดาที่เป็นเบาหวานขณะตั้งครรภ์

พันธบัตร วรินทักษะ, วิรดา ดุลยพัชร์, สมมาตร บำรุงพืช

บทคัดย่อ

วัตถุประสงค์*: เบาหวานขณะตั้งครรภ์เป็นโรคเมตาบอลิซึมที่พบได้บ่อยในสตรีตั้งครรภ์ โดยพบประมาณร้อยละ 20-25 ในภูมิภาคเอเชียตะวันออกเฉียงใต้ โดยการศึกษานี้จะทำการตรวจวัดสัดส่วนการเปลี่ยนแปลงของการไหลของเลือดในหลอดเลือด ductus venosus ของทารกในครรภ์ของสตรีตั้งครรภ์ที่มีภาวะดังกล่าว*

วัสดุและวิธีการ*: การศึกษาไปข้างหน้าของกลุ่มประชากร แบ่งเป็นกลุ่มสตรีตั้งครรภ์ความเสี่ยงต่ำ 76 คนและกลุ่มสตรีตั้งครรภ์ที่เป็นเบาหวานขณะตั้งครรภ์ 36 คน ศึกษาตั้งแต่ มีนาคม 2564 ถึง พฤศจิกายน 2564 โดยทำการตรวจหลอดเลือด Ductus venosus และหลอดเลือดดำสายสะดือของทารกในครรภ์ในช่วงอายุครรภ์ 28-32 สัปดาห์ ด้วย Doppler ultrasound จากนั้นนำข้อมูลที่ได้ไปคำนวณโดย สูตรเทียบสัดส่วนการไหลของหลอดเลือด Ductus venosus หลังจากนั้นติดตามเก็บข้อมูลของทารกในครรภ์หลังคลอดได้แก่ ภาวะแทรกซ้อนก่อนคลอด อายุครรภ์ที่คลอด น้ำหนักแรกคลอด คะแนน Apgar การนอนรักษาตัวในหอผู้ป่วยวิกฤตทารกแรกเกิด การใช้เครื่องช่วยหายใจ ภาวะแทรกซ้อนโดยภาพรวมแรกเกิดจากประชากรทั้งสองกลุ่ม และนำข้อมูลทั้งหมดที่ได้มาวิเคราะห์ข้อมูลทางสถิติ*

ผลการศึกษา*: ในกลุ่มประชากรที่ทำการศึกษาทั้งสองกลุ่มไม่มีความแตกต่างกันในข้อมูลพื้นฐานของประชากร ยกเว้นอายุของมารดาที่ทำการศึกษา จากการเก็บข้อมูลพบว่า ค่าความต่างเฉลี่ยของปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือของกลุ่มที่มารดาเป็นเบาหวานขณะตั้งครรภ์ มีค่าต่ำกว่ากลุ่มควบคุมโดยมีค่า 110.84 ± 36.93 มล./นาที/กก. และ 125.86 ± 36.37 มล./นาที/กก. ตามลำดับ โดยไม่พบการเปลี่ยนแปลงในค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus ที่ร้อยละ 41.34 ± 13.35 ในกลุ่มที่มารดาเป็นเบาหวานขณะตั้งครรภ์ และร้อยละ 40.18 ± 17.31 ในกลุ่มควบคุม ซึ่งไม่แตกต่างกันในเชิงสถิติ (p = 0.70) โดยหลังจากใช้สมการถดถอยหลายตัวแปรแล้วไม่พบความแตกต่างของค่าปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือด Ductus venosus และค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus ในประชากรทั้งสองกลุ่ม นอกจากนั้นยังไม่พบความสัมพันธ์ของการสัดส่วนการเปลี่ยนแปลงการไหลของหลอดเลือด Ductus venosus ต่อผลลัพธ์ของสุขภาพทารกแรกเกิด*

สรุป*: จากการศึกษานี้พบว่า ในกลุ่มมารดาเป็นเบาหวานขณะตั้งครรภ์ที่ควบคุมระดับน้ำตาลได้ดี อาจส่งผลป้องกันการเพิ่มขึ้นของการไหลเวียนของเลือดไปที่ตับของทารกในครรภ์ ซึ่งบ่งชี้จากการที่ไม่พบการเปลี่ยนแปลงที่มีนัยสำคัญของค่าเปรียบเทียบสัดส่วนของการไหลของหลอดเลือด Ductus venosus และค่าปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ*

คำสำคัญ: *เบาหวานขณะตั้งครรภ์, ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือด Ductus venosus, ปริมาณการไหลของเลือดต่อหนึ่งหน่วยเวลาในหลอดเลือดดำสายสะดือ, ผลลัพธ์ของทารกแรกเกิด, สัดส่วนการเปลี่ยนแปลงการไหลของหลอดเลือด Ductus venosus*

Introduction

Gestational diabetes mellitus (GDM) is a common metabolic disorder in pregnancy as it can be identified around 20% to 25% of Southeast Asian pregnant women[1]. Metabolic derangement in GDM patients are characterized by insufficient insulin secretion from pancreatic β-cells[2]. The coexistence of insulin secretory defects and insulin resistance can increase maternal blood glucose levels[3]. According to the Pedersen hypothesis, maternal hyperglycemia leads to an increased glucose transport across the placenta and fetal hyperglycemia[4] The consequence is an accelerated fetal oxidative metabolism, affecting neonatal outcomes[5]. This includes an altered cardiovascular adaptive development[6]. Such fetuses develop an increased umbilical venous flow (UVF), an increased umbilical perfusion of the fetal liver, an enlarged fetal liver, and a low ductus venosus (DV) flow[7-9].

Generally, blood flow from the placenta to the fetus through umbilical vein (UV) is the main source of oxygen and nutrition during fetal life. The fetal hepatic blood flow pattern may be affected by maternal pathological conditions such as maternal diabetes, chronic hypertension, renal disease, and autoimmune disease[10]. The ductus venosus (DV) is a narrow, trumpet-shaped vessel within the fetal liver parenchyma. It is connected to the UV, serving as a physiological vascular shunt that allows oxygenated blood from the placenta to the fetal brain and myocardium. In a normal fetus, the UVF is distributed to the left and the right hepatic lobes at 55% and 20%, respectively. Additionally, 25% of UV blood bypasses the hepatic circulation and directly shunts through the DV[11]. Hence, an assessment of fetal DV shunting may be useful for detecting the impact of maternal diabetes on fetal circulation.

Few studies have evaluated the blood flow pattern through UV and DV during pregnancy. Different distributions of blood flow through UV and DV among fetal growth restriction (FGR), macrosomia in non-diabetic mothers, and normal growth fetuses have been reported[12, 13]. In addition, the association of UV, ductus venosus flow, and DV shunting in diabetic pregnancies has also been studied. Such, an increased DV pulsatility index (PI) in diabetic mothers when compared to low-risk pregnancies, an increased UVF, a reduced DVF, and a decreased DV to UV ratio have been revealed[9, 14].

The increasing fetal UVF and DV shunting ratios in maternal diabetes has been proposed; therefore, these parameters were studied to detect fetal circulation disturbances in well-controlled GDM mothers. This leads to the main objective of this study where the fetal UVF and DV shunting at 28-32 weeks of gestation among well-controlled GDM mothers and uncomplicated pregnant women were determined. Additionally, postnatal outcomes were also gathered, including gestational age (GA) at delivery, birth weight, Apgar score, neonatal intensive care unit admission, ventilator support, and composite adverse outcomes.

Materials and Methods

Study design and participants

This prospective cohort study was conducted in pregnant women who attended the antenatal care clinic before 18 weeks of gestation at Ramathibodi Hospital, Mahidol University, from March 2021 to November 2021. The study was approved by the Institutional Review Board of Ramathibodi Hospital

(COA. MURA2021/90) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

The sample size was calculated based on the data of the study, which found 18% of the mean DV shunting in maternal diabetes[9]. With a two-sample independent formula using a standard deviation (SD) of 12.58 and 90% power of the study, at least 33 participants in the GDM group and 67 participants in the control group were needed. The two-to-one allocation ratios of the GDM and the control groups were calculated.

All pregnancy dating was performed using standard fetal biometry ultrasonography according to the American College of Obstetricians and Gynecologists (ACOG) 2017 guidelines[15]. All women between 18 and 22 weeks of gestation were screened for any fetal anomaly according to the American Institute of Ultrasound in Medicine (AIUM) 2013 protocol[16].

GDM at our institution is diagnosed using universal screening with fasting blood sugar (FBS) and glycosylated hemoglobin (HbA1c) administered to all pregnant women regardless of the risk factors at the first antenatal care (ANC) visit. The value of FBS ≥ 92 mg/dL and < 126 mg/dL were considered positive for GDM. Among the pregnant women who had normal GDM screening at the first ANC, a 75 g oral glucose tolerance test (OGTT) was performed at 24-28 weeks of gestation. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Group (IADPSG)[17], and the criteria for GDM diagnosis were established when any single threshold value was met or exceeded as follows:

- Fasting value, ≥ 92 mg/dl
- 1-hour value, ≥ 180 mg/dL
- 2-hour value, ≥ 153 mg/dL

All pregnant women diagnosed with GDM were recommended for nutritional planning and management with self-monitoring blood glucose (SMBG) level surveillance[18, 19]. Two weeks after the GDM diagnosis, poor glycemic controlled GDM was defined as 50% or more of SMBG level records, which exceeded the optimal goal[20].

The inclusion criteria were established for all singleton pregnancies of women aged 20 years or older, at 18-22 weeks of gestation, who had been confirmed by early ultrasound examination before 18 weeks of gestation and were willing to participate. The informed consent was obtained from all participants. The pregnant women with pre-gestational diabetes or with fetal, placental, and umbilical cord structural anomalies or FGR, according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) criteria 2020[21], were excluded at the time of diagnosis before being recruited to any group. Those who could not obtain Doppler studies of UV and/or DV and had incomplete clinical data acquisition and unwillingness to participate were also excluded. Participants were categorized into the control group and the GDM group. The control group consisted of women with uncomplicated pregnancies who were willing to participate and had no underlying diseases diagnosed before pregnancy.

Outcome measures

All participants at 28-32 weeks' gestation underwent the ultrasonographic examination for the DVF and UVF using GE Voluson® E10 (GE Healthcare, Chicago, IL, US) with a curvilinear transducer. After fetal size and deepest vertical pocket (DVP) were measured, the diameters of the UV, the DV, and their flow velocimetry according to the ISUOG 2013 guideline[22] of standard Doppler study. The UVF and DVF were obtained as follows:

1. UV diameter, under the magnification of the image > 30%, was measured perpendicularly from inner wall to inner wall of UV lumen at the straight portion of the intra-abdominal UV before the first branching of the portal vein from a transverse view of the upper abdomen[11] (Fig. 1A). The UV diameter was calculated as the average of three measurements[23].

2. UVF velocity was obtained by pulsed-wave Doppler during fetal quiescence for 2-4 s, requiring an insonation angle close to zero or less than 15° with

angle correction, with the sample volume covering the width of UV (Fig. 1B). The reported velocity of the UVF was derived from the average of two measurements. UVF, along with absolute UVF (mL/min) and corrected UVF by estimated fetal weight (EFW) (UVF/kg), was calculated using the following formula:[24]

UVF = 0.5 × maximum venous time-averaged velocity (TA max) (cm/s) × 3.14 × (UV diameter/2)^2 (cm^2) × 60(s)

1. DV diameter was measured from the inner wall of the DV to the inner wall of the DV lumen at the isthmus (Fig. 1C) in accordance with a previous standardized technique[25, 26]. The inner diameter of the DV to reduce random error, the procedure was usually repeated three times, and the calculated mean diameter was used for statistical analysis[23].

2. The DVF velocity was recorded in a separate axial direction using sagittal insonation, rarely in an oblique transection of the fetal abdomen with an expanded sample volume covering the isthmus of the DV. The angle of insonation was kept as low as possible and not much greater than 15° (Fig. 1D). The velocity was recorded for 2-4 s during fetal quiescence. The reported velocity of the DVF was derived from the average of two measurements.

DVF, including absolute DVF (mL/min) and corrected DVF for EFW (DVF/kg), was calculated using the formula below[27].

DVF = 0.7 x the venous time-averaged maximum velocity (TA max) (cm/s) × 3.14 × (DV diameter/2)^2 (cm^2) × 60(s)

The DV shunting was calculated from the formula below[9].

DV shunting (%) = DVF/UVF x 100

The Doppler study above was performed by Maternal and Fetal Medicine specialists and Maternal and Fetal Medicine fellow. DV/UV diameter and flow ratios were assessed in 17 participants (3 times per each participant) for inter-observer agreements among 3 investigators.

All participants were scheduled for a follow-up according to the standard care for maternal diabetes at Ramathibodi Hospital. The participants diagnosed with fetal complications such as FGR, oligohydramnios, and abnormal fetal testing on fetal surveillance were scheduled for a follow-up according to the management guidelines for specific diseases

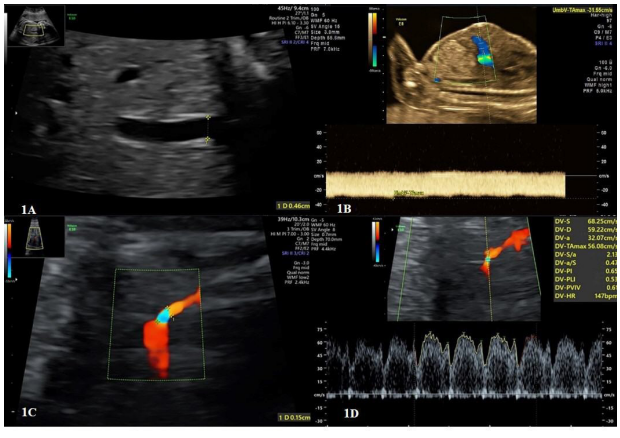

Fig. 1. UVF and DVF measurement. (1A) UV diameter is measured perpendicularly from the inner wall to the inner wall of the UV lumen, at the straight portion of the intra-abdominal UV before the first branching of the portal vein from a transverse view of the upper abdomen, under the magnification of the image > 30%. (1B) UVF velocity is obtained by pulsed-wave Doppler during fetal quiescence for 2 to 4 seconds, requiring the insonation angle close to zero or less than 15 degrees with angle correction. (1C) DV diameter is measured from the inner wall to the inner wall of the DV lumen at the isthmus. (1D) DVF velocity is obtained in sagittal insonation during fetal quiescence with an expanded sample volume covering the isthmus of the DV, with an insonation angle less than 15 degrees.
UVF: umbilical venous flow, DVF: ductus venous flow, UV: umbilical vein, DV: ductus venosus.

The main outcome was the comparison of DV shunting (%) between the GDM group and the control group. Subsequently, maternal age, GA, blood pressure, pregnancy, and neonatal outcomes were collected and analyzed, including antenatal complications, GA at delivery, birth weight, Apgar score, NICU admission, ventilator support, and neonatal morbidity for evaluating the correlation between DV shunting and postnatal outcomes.

Statistical analysis

The data analysis was performed using Stata version 17 (StataCorp LLC., College Station, TX, US). Intra-class correlations were performed using a two-way mixed-effects model to evaluate the consistency of agreements. Inter-observer agreements of DV/UV diameter and flow ratios were assessed using the Bland-Altman plot (Fig. 2) among 17 participants. The mean DVF and UVF of fetuses with maternal diabetes were compared with those of low-risk fetuses using an independent sample t-test. The associations between each ultrasound measurement as a dependent variable and maternal diabetes as an independent variable, with an adjustment for maternal age and GA, were determined using multiple linear regression. The neonatal outcomes of the maternal diabetes group, including GA at delivery, birth weight, Apgar score, NICU admission, ventilator support, and composite adverse outcomes, were compared with those of low-risk fetuses using independent sample t-test, chi-square test, or Fisher's exact test.

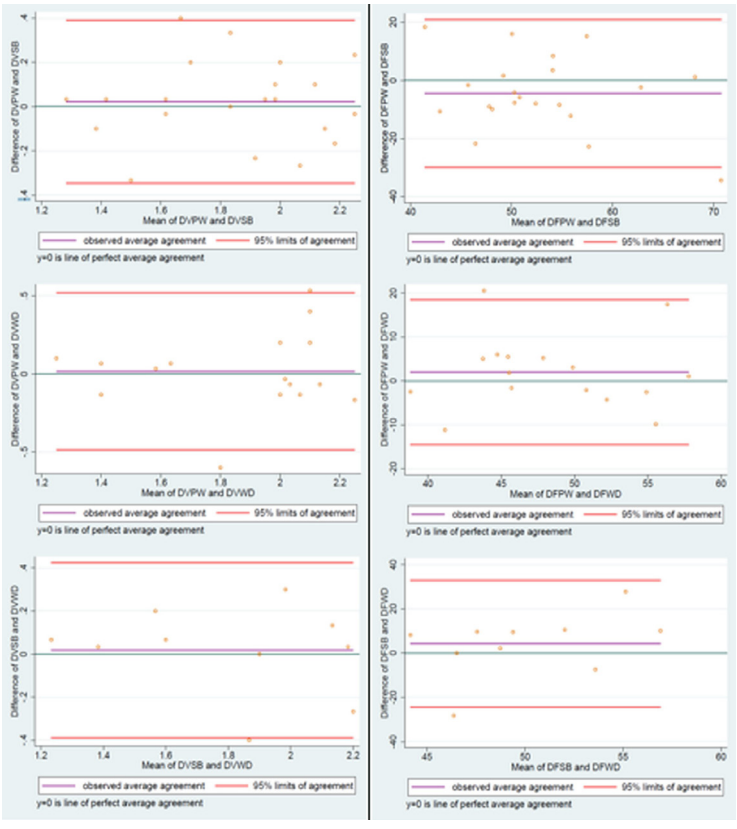

Fig. 2. Bland–Altman plot showed a difference in values within the 95% limit of agreement of inter-observer agreement of DV diameter (1A), DVF TA max (1B), UV diameter (1C) and UV TA max (1D).

DVF: ductus venosus flow, UV: umbilical vein, TA: time-averaged

Results

Two hundred and fifty-eight pregnant women were enrolled, but 139 women were excluded (Fig. 3). Therefore, DVF, UVF, and pregnancy outcomes were examined in 119 pregnant women, consist of 76 uncomplicated singleton pregnancies in the control group and 43 GDM pregnant women. Seven women in the GDM group were excluded because Doppler studies could not be performed. Ultimately, 76 participants in the control group and 36 in the GDM group who were diagnosed at the first antenatal care (ANC) visit 25 women and a 75 g oral glucose tolerance test at 24-28 weeks of gestation 11 women followed postnatal outcomes. Intra-observer reliability was assessed using a two-way mixed-effects model revealing that DV diameter, DVF time-averaged maximum velocity, UV diameter and UV (TA) max had the intra-class correlations coefficient (ICC) at 0.68, 0.59, 0.92 and 0.8, respectively. In addition, the inter-observer agreement of DV diameter, DVF TA max, UV diameter, and UV TA max exhibited by the Bland-Altman plot showed a difference in values within the 95% limit of agreement (Fig. 2).

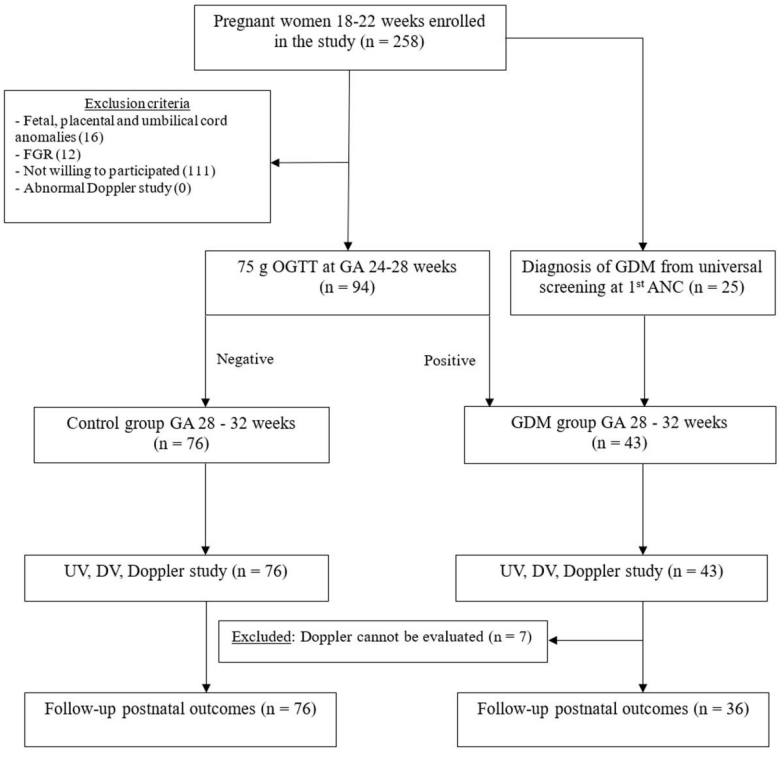

Fig. 3. Study flow diagram.

FGR: fetal growth restriction, OGTT: oral glucose tolerance test, GA: gestational age, GDM: gestational diabetes mellitus, ANC: antenatal care, UV: umbilical vein, DV: ductus venosus.

Table 1 presents the baseline characteristics of the participants. The baseline characteristics of both groups were not significantly different except for the mean maternal age. The mean age of the diabetic group was remarkably higher than that of the control group (33.48 ± 4.66 years vs 30.76 ± 5.84 years, p = 0.016).

Table 1. Baseline characteristics.

Characteristics	GDM group (n = 36)	Control group (n = 76)	p value[a]
Age (years)	33.48 ± 4.66	30.76 ± 5.84	0.016
Gravida			
Nulliparous	15 (41.7)	30 (39.5)	0.168
Multiparous	21 (58.3)	46 (60.5)	
Number of term delivery			
0	19 (52.8)	43 (56.6)	0.099
1	11 (30.6)	28 (36.8)	
2	3 (8.3)	5 (6.6)	
3	3 (8.3)	0 (0.0)	
History of preterm delivery			
1	0 (0.0)	2 (2.6)	1.000
GA (days)	203.19 ± 5.53	204.67 ± 6.62	0.245
Pre-pregnant BMI (kg/m^2)	23.13 ± 4.30	21.87 ± 3.5	0.107
Current BMI (kg/m^2)	25.42 ± 4.47	25.38 ± 3.85	0.957

GDM: gestational diabetes mellitus, GA: gestational age, BMI: body mass index.
Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
[a] p values correspond to the independent samples t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test.

The DV diameter, DV TA max, absolute DVF, and adjusted DVF were slightly lower in the GDM group than in the control group. However, the differences were not statistically significant. When we assessed the DV/UV diameter and flow ratios, no significant differences were observed between the diabetic and the control groups. The UV diameter, DV diameter, UVF, DVF, DV/UV diameter, and DVF/UVF ratios are listed in Table 2.

Table 3 shows the results of the multivariate analyses with the adjusted maternal age and GA. The mean difference in UVF in the GDM group was slightly lower than that in the control group at 110.84 ± 36.93 mL/min/kg and 125.86 ± 36.37 mL/min/kg, respectively. However, the difference was not statistically significant. Likewise, no significant difference was observed between DVF and DV shunting.

Table 2. Comparison of primary outcomes between the GDM and control group.

Parameter	GDM group (n = 36)	Control group (n = 76)	p value[a]
EFW (g)	1,280.14 ± 184.98	1,329.16 ± 220.08	0.25
DV diameter (mm)	1.91 ± 0.27	1.99 ± 0.28	0.15
DV Tmax (cm/s)	46.48 ± 9.28	47.9 ± 11.41	0.51
DV flow (ml/min)	56.38 ± 18.01	64.31 ± 26.76	0.11
DV flow/kg (ml/min/kg)	44.4 ± 15.22	49.36 ± 22.54	0.23
UV Diameter (mm)	5.01 ± 0.65	5.23 ± 0.69	0.11
UV TA max (cm/s)	23.86 ± 4.8	25.53 ± 5.48	0.12
UV flow (mL/min)	140.91 ± 36.93	165.88 ± 52.67	0.012
UV flow/kg (mL/min/kg)	110.84 ± 29.18	125.86 ± 36.37	0.032
DV/UV diameter ratio (%)	38.35 ± 5.37	38.54 ± 7.19	0.88
DV shunting (%)	41.34 ± 13.35	40.18 ± 17.31	0.72

g: gram, mm: millimeter, cm/s: centimeter/second, mL: milliliter, min: minute, kg: kilogram, EFW: estimated fetal weight, DV: ductus venosus, UV: umbilical vein.
Data are presented as mean ± standard deviation or median (interquartile range).
[a] Independent samples t-test.

Table 3. Multivariable analysis using multiple linear regression analysis adjusted for age and GA.

Parameter	Adjusted mean difference between GDM and control group	95% confidence interval	p value
DV diameter (mm)	- 0.036	(- 0.149 to 0.077)	0.527
DV Tmax (cm/s)	- 1.277	(- 5.828 to 3.274)	0.579
DV flow (mL/min)	- 5.251	(- 15.401 to 4.898)	0.307
DV flow/kg (mL/min/kg)	- 4.966	(- 13.462 to 3.531)	0.249
UV Diameter (mm)	- 0.172	(- 0.450 to 0.106)	0.223
UV TA max (cm/s)	- 0.999	(- 3.181 to 1.184)	0.366
UV flow (mL/min)	- 17.604	(- 37.132 to 1.924)	0.077
UV flow/kg (mL/min/kg)	- 14.296	(- 28.645 to 0.053)	0.051
DV/UV diameter ratio (%)	0.369	(- 2.421 to 3.160)	0.794
DV shunting (%)	- 1.112	(- 9.807 to 7.583)	0.800

GA: gestational age, g: gram, mm: millimeter, cm/s: centimeter/second, mL: milliliter, min: minute, kg: kilogram, EFW: estimated fetal weight, DV: ductus venosus, UV: umbilical vein.

The pregnancy outcomes revealed five neonates in the GDM group with unfavorable outcomes, including the need for ventilator support (n = 2), asymptomatic hypoglycemia (n = 2), and persistent pulmonary hypertension (n = 1). No such event was observed in neonates in the control group. Nevertheless, the differences in these features were not statistically significant, nor were the other perinatal outcomes (Table 4).

Table 4. Comparison of secondary outcomes between the GDM and control group.

Outcome	GDM group (n = 36)	Control group (n = 76)	p value[a]
Delivery			
Preterm	2 (5.6)	2 (2.6)	0.593
Term	34 (94.4)	74 (97.4)	
Birth weight (g)	3,074.33 ± 427.98	3,182.55 ± 373.49	0.175
Mode of delivery			
Vaginal delivery	24 (66.7)	45 (59.2)	0.449
Cesarean section	12 (33.3)	31 (40.8)	
Apgar score in the 5th minute			
≥ 7	36 (100.0)	76 (100.0)	
Ventilator support	2 (5.6)	0 (0.0)	0.101
Composite outcomes	5 (13.9)	7 (9.2)	0.455
TTNB	1 (2.8)	4 (5.3)	1.000
SGA	1 (2.8)	3 (4.0)	1.000
LGA	1 (2.8)	0 (0.0)	0.321
Asymptomatic hypoglycemia	2 (5.6)	0 (0.0)	0.101
Persistent pulmonary hypertension	1 (2.8)	0 (0.0)	0.321

g: gram, TTNB: transient tachypnea of the newborn, SGA: small for gestational age, LGA: large for gestational age.
Data are presented as number (%) or mean ± standard deviation.
[a] p value corresponds to independent samples t-test, chi-square test, or Fisher's exact test.

Discussion

This study evaluated fetal UVF, DVF, and DV shunting between well-controlled GDM and uncomplicated pregnancies during 28-32 weeks of gestation. Only a significantly lower UVF was observed in the GDM group than in the control group. The insight gained from this study was that, in well-controlled GDM, the distribution of umbilical venous flow to the fetal liver or DV was not altered.

Several studies have examined fetal UVF and DVF in high-risk pregnancies[12-14]. Nevertheless, the alteration of the DVF was observed exclusively in

severely compromised fetuses[13]. Limited evidence of DV shunting assessed in fetuses with maternal diabetes has been previously provided; and some studies have been conducted on various types of maternal diabetes, including pre-gestational DM, well-controlled GDM, and GDM treated with insulin[9, 28]. One study assessed the diameters of the UV, DV, and DV PI in pre-gestational DM and GDM compared with normal reference values of pregnant women without any risks between 28 and 36 weeks of gestation[14]. The only abnormal finding in this study was an increased DV PI in both pre-existing, insulin-dependent and gestational diabetes groups compared to low-risk pregnancies. Another study compared UVF, DVF, and DV shunting in fetuses with pre-gestational DM and low-risk pregnancies[9]. It demonstrated a significantly increased UVF and reduced DVF, resulting in decreased DV shunting. Likewise, a recently published study regarding DV shunting in the GDM group managed by diet control, with or without insulin therapy[28], demonstrated a significantly reduced DV diameter, absolute DVF, and DV shunting in fetuses of GDM mothers compared to low-risk pregnant ones.

The present study found no statistically significant differences between DVF and DV shunting, but significantly lower UVF was found in well-controlled GDM pregnancies than in low-risk pregnancies. Our findings differed from previously published studies that showed reduced DVF and DV shunting in the maternal diabetes groups[1, 12-14, 29]. Those studies included pregnancies with pre-gestational DM or GDM with insulin therapy. Pregnancies diagnosed with pre-gestational DM or GDM receiving insulin therapy might be readily affected by abnormal glucose metabolism, especially in maternal diabetes with suboptimal blood glucose control[30]. Detrimental effects on the fetus may occur during early pregnancy; and consequently, a decrease in DV shunting might be detected because of the fetal compensatory process to acquire sufficient oxygen supply[31].

Nevertheless, previous studies found that increased distribution of UVF to the fetal liver contributed to higher birth weight in pre-gestational diabetic pregnant women due to increased insulin-like growth factor 1 and 2 production and induced somatic growth of the fetus[12-14, 29]. Additionally, there is an evidence that UVF studied in early and late gestations is associated with fetal macrosomia[29, 32, 33]. This might be explained by an increase in UVF due to the increased placental size in the first trimester[29, 32, 33]. The most recent study demonstrated a reduction in DV diameter, DVF, and DV shunting among women with GDM[28]. They recruited a large number of maternal GDM women (31.4%) who required insulin treatment. No data was derived from a subgroup analysis of fetal DV shunting between the diet control GDM and the GDM with insulin therapy. Theoretically, in the fetus of GDM pregnancies, there may be liver enlargement, with more umbilical blood distributed to the fetal liver at the expense of the DV flow. This decreased DV shunting is expected to be more pronounced in cases with the fetuses' poor glycemic control, which is associated with liver enlargement, and their outcomes such as large for gestational age infants or macrosomia. However, this study did not find such effects, possibly because it included only the cases with well-controlled blood glucose levels. Consequently, no changes in blood distribution to the liver were observed.

Moreover, the composite neonatal outcomes did not differ significantly between these two groups, indicating good glycemic control of the participants in the GDM group.

The strengths of our study included the examination of DV shunting at 28-32 weeks of gestation and the observation that the trend of DV shunting remained relatively constant across gestational ages during this period[26]. However, there are several limitations to note: 1. We only evaluated UV-DV circulation once at 28-32 weeks, so any changes occurring other pregnancy period were not assessed. This means that our study did not include the data on well-controlled cases beyond 32 weeks of gestation, the time when a marked reduction of DV flow has been shown to occur in pre-gestational

diabetes mellitus[9]. 2. The intra-observer variability contributes to the total variation of measurements and in this study, this variability was moderate. Hence, further evaluation of reproducibility is needed in future studies. We acknowledge that a stricter measurement protocol including higher numbers of repeat measurements, particularly for the diameter of the DV, would have reduced random error and increased the likelihood of exposing differences[23]. 3. The small size of the DV makes it particularly susceptible to measurement errors. The high DV flow rates observed may be due to the measurement technique. Using color Doppler can affect the spatial representation of the vessel wall, potentially leading to overestimation of diameters. Nevertheless, assuming the technique was consistent throughout the study, the comparison between the two groups can still be considered valid.

Conclusion

This study suggested that good control of maternal GDM may prevent an increase in fetal hepatic blood flow, as indicated by no significant changes of DV shunting and UVF.

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Potential conflicts of interest

The author declares no conflicts of interest.

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GYNAECOLOGY

Effectiveness of Preoperative Oral Diazepam for Reducing Anxiety during Loop Electrosurgical Excision Procedure: A double-blind randomized controlled trial

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ABSTRACT

Objectives: To compare the pre- and postoperative anxiety score by State-Trait Anxiety Inventory (STAI) and visual analogue scale of anxiety (VAS-A) of the patients who received preoperative oral diazepam with those who received a placebo during loop electrosurgical excision procedure (LEEP).

Materials and Methods: This study is a double-blind, randomized controlled trial. There were 156 patients enrolled and allocated; group 1 received an oral diazepam 10 mg (n = 78) and group 2 received a placebo (n = 78) 1 hour before the operation. Both groups had received the same local anesthesia and standard care. Pre- and postoperative anxiety were measured by STAI and VAS-A immediately before the operation and, again, one hour after the operation. Pain score was measured by visual analogue scale of pain 30 minutes after the operation. All anxiety and pain scores were compared for both groups using an unpaired t test.

Results: The baseline characteristics were similar between groups. The preoperative diazepam and placebo group had STAI scores of 45.60 versus 44.02, respectively with the mean difference -1.57 (95% confidence interval -4.36,1.20) without a significant difference. Also, the postoperative anxiety score, pain score, heart rate and mean arterial pressure were not significantly different.

Conclusion: Preoperative oral diazepam 10 mg administered one hour before operation did not decrease the pre- and postoperative anxiety or pain levels in LEEP. Other treatments are required and should be the subject of further studies.

Keywords: diazepam, anxiety, loop electrosurgical excision procedure, State-Trait Anxiety Inventory, visual analogue scale of anxiety.

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ประสิทธิผลของการใช้ยาไดอะซิแพมในรูปแบบกินก่อนทำหัตถการเพื่อลดความกังวลขณะทำการผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้า: การศึกษาเชิงทดลองแบบสุ่มปกปิดสองทาง

ศตวรรษ เจริญวงศ์, เสาวณีย์ ตั้งมโนวุฒิกุล, เมธา ทรงธรรมวัฒน์, ศรีสุดา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์

บทคัดย่อ

วัตถุประสงค์: *เปรียบเทียบระดับค่าคะแนนความกังวลของผู้ป่วยที่ได้รับยาไดอะซิแพมในรูปแบบกินก่อนผ่าตัดและยาหลอกขณะผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้า*

วัสดุและวิธีการ: *การศึกษาทดลองแบบสุ่ม โดยผู้ป่วยที่มารับการผ่าตัดปากมดลูกด้วยห่วงลวดไฟฟ้าจำนวน 156 คนเข้าร่วมการศึกษา และได้รับการจัดสรรให้อยู่ในกลุ่มหนึ่งในสองกลุ่ม กลุ่มที่ 1 ได้รับยาไดอะซีแพมในรูปแบบรับประทาน ขนาด 10 มิลลิกรัม (n = 78), กลุ่มที่ 2 รับยาหลอกซึ่งลักษณะเม็ดคล้ายกัน (n = 78) ก่อนทำหัตถการ 1 ชั่วโมง โดยทั้ง 2 กลุ่มได้รับยาชาเฉพาะที่และการรักษาตามมาตรฐานที่เหมือนกัน ทำการวัดค่าความวิตกกังวลก่อนเริ่ม และหลังการทำหัตถการ 1 ชั่วโมงด้วย State-Trait anxiety inventory (STAI) และ Visual Analogue Scale of Anxiety และวัดคะแนนความเจ็บปวดที่ 30 นาทีหลังทำหัตถการ ด้วย Visual Analogue Scale of Pain เปรียบเทียบค่าคะแนนความกังวลระหว่างกลุ่มโดย unpaired t test*

ผลการศึกษา: *ไม่มีความแตกต่างของลักษณะทางคลินิกพื้นฐานก่อนการผ่าตัดระหว่างทั้งสองกลุ่ม ค่าเฉลี่ย STAI ก่อนเริ่มการผ่าตัดระหว่าง 2 กลุ่มเท่ากับ 45.60 และ 44.02 โดยค่าเฉลี่ยความแตกต่างเท่ากับ -1.57 (ช่วงความเชื่อมั่น 95% -4.36,1.20) ซึ่งไม่มีความแตกต่างกันทางสถิติ และค่าคะแนนความกังวลหลังทำหัตถการ 1 ชั่วโมง คะแนนความปวด อัตราการเต้นของหัวใจและความดันเลือดเฉลี่ย ไม่พบมีความแตกต่างกันอย่างมีนัยยะสำคัญทางสถิติระหว่างกลุ่ม*

สรุป: *การรับประทานยาไดอะซิแพม 10 มิลลิกรัม 1 ชั่วโมงก่อนผ่าตัด ไม่สามารถลดความวิตกกังวลหรือความเจ็บปวดในการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า การรักษาด้วยวิธีอื่นเพื่อลดความกังวลยังคงจำเป็นและต้องมีการศึกษาเพิ่มเติมต่อไป*

คำสำคัญ: *ไดอะซิแพม, ความกังวล, การตัดปากมดลูกด้วยห่วงลวดไฟฟ้า, State-Trait Anxiety Inventory, visual analogue scale of anxiety*

Introduction

Cervical cancer is the third most common cause of death for cancer patients especially in the developing countries[1]. Precancerous finding is the aim of worldwide screening program to eliminate cervical cancer around the world. Loop electrosurgical excision procedure (LEEP) is the most popular method for the diagnosis and treatment of cervical intraepithelial neoplasia (CIN) lesion. The World Health Organization (WHO) recommends LEEP for women who have histologically CIN2+ disease[2].

Receiving bad news about abnormal cervical cytology and fear of treatment procedures such as colposcopy and LEEP can cause significant anxiety and psychological distress, mostly due to fear of having cancer and an unclear understanding of the treatment process[3-5]. Some patients feel nervous and tend to have insomnia[6-7] and it is well established that the increase of anxiety levels is associated with worse pain during operation[5]. Several methods, both pharmacological and non-pharmacological, have been used for decreasing anxiety levels which aim to reduce hemodynamic instability due to stress induced during surgery. Diazepam is a common anxiolytic drug that has been used to decrease tension before and during surgery[8], Diazepam is a long-acting benzodiazepine. This drug affects the central nervous system, which can help with sedation and hypnosis. However, its effectiveness in the preoperative stages of a LEEP procedure has not been studied. Therefore, the aim of the present research was to compare the anxiety scores of the patients who received preoperative oral diazepam with patients who were given a placebo before undergoing a LEEP.

Materials and Methods

This study was a randomized controlled trial conducted at a tertiary care hospital. The study protocol was approved by Udonthani Hospital Ethical Committee on human research (number 123/2566) and was registered in Thaiclinicaltrials.org (TCTR20240630006). The study period was from January 2024 to August 2024. The inclusion criteria were women aged 18 years or older, who have abnormal cervical cytology with an indication for LEEP according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guideline (2019)[9] for abnormal cervical cancer screening tests and cancer precursors. The exclusion criteria were as follows: (1) diazepam allergy; (2) pregnancy; (3) cervical and vaginal infection; (4) taking diazepam or benzodiazepine drug less than 24 hours before the procedure; (5) cirrhosis (6) chronic kidney disease stage 3 or higher; (7) unstable blood pressure; (8) depression, central nervous system depression, or other mental disease; (9) myasthenia gravis, attention deficit, hyperactivity disorder, or chronic obstructive pulmonary disease; (10) cardiovascular events such as stroke, cerebral ischemia, or myocardial infarction before 6 month (11) visual impairment.

The primary outcome was to compare both pre- and postoperative anxiety score by State- Trait Anxiety Inventory (STAI)[10] and visual analogue scale of anxiety (VAS-A)[11] immediately before the operation (1 hour after taking the intervention) between treatment and placebo groups. The secondary outcomes were to compare 1) anxiety scale at 30 minutes post-operation 2) visual analogue scale of pain (VAS-P) at 30 minutes postoperation and 3) the mean arterial pressure and heart rate at preoperative, intraoperative and postoperative times between groups.

All participants were informed about the disease and surgical procedure before their participation in this study. After enrollment, the participants were allocated sequentially into one of two groups by research assistants using the computer generated randomization number in opaque sealed envelopes. Group 1 received an oral diazepam 10 mg; group 2 received the placebo in similar packaging one hour before the procedure. Both intervention packages were prepared by a pharmacist who was not involved with the data

collection process. The questionnaires were answered by the participants before LEEP (1 hour after intervention). The questionnaire was composed of baseline characteristics, STAI, VAS-A, VAS-P, heart rate, and mean arterial blood pressure. STAI designed by Spielberger[10] in 1989, was translated to a Thai version, validated and tested, by Kotchapakdee et al[12]. It consists of 20 questions, 10 positive questions and 10 negative questions. The participants were required to complete the questionnaires by themselves, the possible scores range from 20 to 80. A high score indicates a high level of anxiety. The anxiety score was divided into 3 groups: mild anxiety (20-40 points), moderate anxiety (41- 60 points) and severe anxiety (61-80 points)[12]. The VAS-A and VAS-P were both comprised of a 10 cm line where the participant marked her degree of pain and anxiety, 0 cm indicates "no pain or no anxiety", 10 cm indicates "maximum pain or anxiety". We used separate scales of pain and anxiety. The VAS-P scale for pain was rated 0 to 4 mm was classified as no pain; 5 to 44 mm was mild pain; 45 to 74 mm was moderate pain; and 75 to 100 mm was severe pain[13-14]. The anxiety levels of the participants were measured before intervention, and again at 30 minutes after the operation. The pain score during the operation was retrospectively measured at 30 minutes after operation. Heart rate and mean arterial blood pressure were recorded at 1 hour before operation, during the operation and again 30 minutes after operation.

LEEP was performed by medical residents and staff of Obstetrics and Gynecology, Udonthani Hospital. All LEEP was performed in operative room. The participant was placed in the lithotomy position. Preoperative vaginal cleansing was done using povidone iodine. The LEEP machine was a monopolar electrosurgery machine. The operators chose the size of loop depending on the cervical size. All participants were anesthetized by paracervical block using 10% lidocaine without adrenaline. Cervical tissue was excised by cutting mode and bleeding was stopped by coagulation mode, then Monsel's solution was applied. Tampon packing was used in cases that minimal bleeding remained. After LEEP, the participants were observed for 1 hour in the postoperative room.

The sample size was calculated based on Levandoski et al study data[15]. The N4studies application was used for the calculation using the formula of a randomized controlled study[16]. The mean STAI of the treatment group was 38.13 and the standard deviation was 6.94 and the control group was 41.91 with a standard deviation of 8.88[14] with the 0.05 alpha error and 0.2 beta error. The calculated sample size was 70 patients in each group. Assuming a 10% dropout rate, 78 patients per group were included in this study.

Statistical analyses were performed using STATA statistical program version 13. Continuous data was reported as the mean and standard deviation. The comparison of the continuous data from both groups was examined by the unpaired t-test. Categorical data shown as the number and percentage. The comparison of the categorical data between groups was examined by Pearson chi-square test or Fisher exact test. P values < 0.05 was used for statistically significant level.

Results

There were 157 patients who were enrolled in this study, one patient was excluded due to taking diazepam within 24 hours before the procedure. After receiving their written consent, 78 patients were randomly assigned to the diazepam group and 78 patients to the placebo group. All 156 patients completed the intervention process and were included in the statistical analysis. The consort diagram is shown in Fig. 1. The baseline characteristics, including age, body weight, Height, BMI, underlying diseases, smoking, alcohol drinking, history of abortion, LEEP indication, and operative time were not significantly different between groups. The details of both group's characteristics are shown in Table 1.

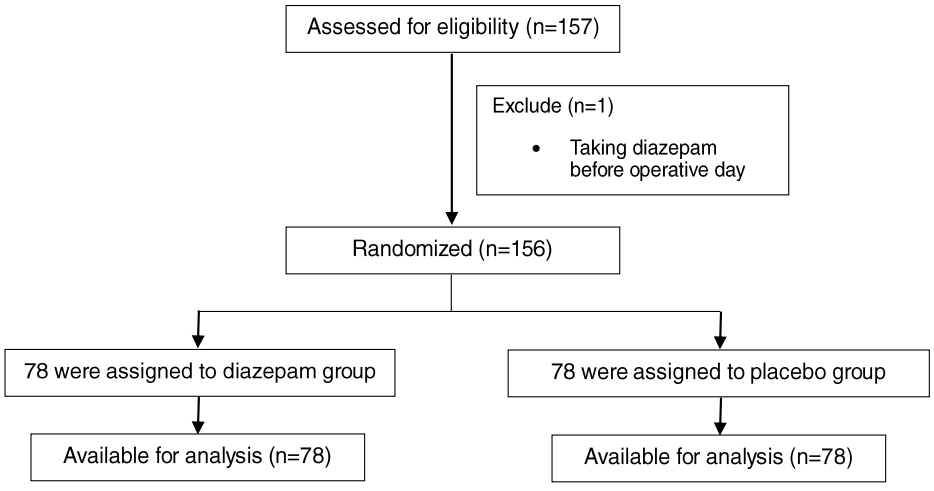

Fig. 1. The percentage of endometrial carcinoma and endometrial intraepithelial neoplasia in each age group.

Table 1. Baseline characteristics.

Characteristic	Group		p value*
	Diazepam (n = 78)	Placebo (n = 78)	
Age (years), mean ± SD	39.41 ± 9.15	41.47 ± 9.03	0.158
Body weight (kg), mean ± SD	58.70 ± 10.47	61.60 ± 12.47	0.118
Height (cm), mean ± SD	157.42 ± 5.31	156.97 ± 5.97	0.620
BMI (kg), mean ± SD	23.71 ± 4.29	24.91 ± 4.33	0.086
Underlying diseases			
Diabetic mellitus, n (%)	1 (1.28%)	5 (6.41%)	0.210
Hypertension	3 (3.85%)	2 (2.56%)	1.000
Asthma	1 (1.28%)	2 (2.56%)	1.000
Smoking	4 (5.13%)	1 (1.28%)	0.367
Alcohol drinking	18 (23.07%)	14 (17.95%)	0.428
History of abortion	14 (17.95%)	23 (29.49%)	0.090
LEEP indication			
HSIL	75 (96.15%)	74 (93.59%)	0.369
Cervical cancer	1 (1.28%)	3 (3.85%)	
Other	2 (2.56%)	1 (1.28%)	
Operative time (min)	13. 07 ± 4.57	14.19 ± 7.18	0.249

SD: standard deviation, min: minutes, kg: kilogram, cm: centimeter, BMI: body mass index, LEEP: loop electrosurgical excision procedure, HSIL: high-grade squamous intraepithelial lesion

* p value was calculated by unpaired t-test, Pearson chi square or Fisher's exact test

Preoperative STAI and VAS-A were not significantly different between oral diazepam and placebo groups (mean difference -1.57, 95% CI -4.36,1.20 by STAI and 1.79, 95% CI -4.36,1.20 by VAS-A). The mean preoperative anxiety scores of both groups were in the moderate anxiety level.

Postoperative STAI and VAS-A were not significantly different between oral diazepam and placebo groups (mean difference -1.89, 95% CI -5.26,1.46 by STAI and 0.38, 95% CI -4.36,1.20 by VAS-A). The mean postoperative anxiety scores of both groups were in the mild anxiety level and markedly decreased from the preoperative anxiety level.

The mean pain score with VAS-P in each group was not significantly different (mean difference -0.25, 95% CI -6.83,6.32). Both postoperative pain levels in each group were mild pain. Both heart rate and mean arterial pressure at any time of operation were not significantly different between groups (Table 2).

Table 2. Study outcomes.

Result	Group		mean difference (95%CI) p value*
	Diazepam (n = 78) (mean ± SD)	Placebo (n = 78) (mean ± SD)	
Pre-operative outcomes			
Anxiety score with STAI	45.60 ± 8.80	44.02 ± 8.74	-1.57 (-4.36, 1.20) 0.264
Anxiety score with VAS-A (mm)	57.94 ± 18.73	59.74 ± 21.01	1.79 (-4.50, 8.09) 0.574
Heart rate (bpm)	83.24 ± 14.61	83.46 ± 14.58	0.27 (-4.39, 4.83) 0.925
Mean arterial blood pressure (mmHg)	94.59 ± 13.99	95.28 ± 14.18	0.68 (-3.79, 5.17) 0.762
Intra-operative outcomes			
Heart rate (bpm)	77.96 ± 11.56	78.74 ± 12.24	0.78 (-2.98, 4.54) 0.682
Mean arterial blood pressure (mmHg)	90.94 ± 10.99	91.76 ± 12.55	0.82 (-2.91, 4.55) 0.664
Post-operative outcomes			
Anxiety score with STAI	35.37 ± 11.48	33.47 ± 9.70	-1.89 (-5.26,1.46) 0.266
Anxiety score with VAS-A	23.33 ± 22.19	23.71 ± 20.13	0.38 (-6.31, 7.08) 0.909
Pain score with VAS-P (mm)	22.56 ± 22.70	22.30 ± 18.72	-0.25 (-6.83,6.32) 0.938
Heart rate (bpm)	77.34 ± 9.91	78.30 ± 10.80	0.96 (-2.31, 4.24) 0.563
Mean arterial blood pressure (mmHg)	89.37 ± 14.21	90.93 ± 10.91	(-2.46, 5.57) 0.444

CI: confidence interval, SD: standard deviation, STAI: The state trait anxiety inventory, VAS-A: visual analogue scale of

Discussion

The present study showed that preoperative 10 mg oral diazepam at one hour before operation did not significantly reduce the pre and postoperative STAI and VAS-A and VAS-P score. The mean anxiety scores in this study were moderate anxiety in preoperative time and mild anxiety in postoperative time. The mean VAS-P was mild.

The result of this study was compatible with Nimmaanrat et al study[17] at Prince Songkla University Hospital which reported that 5-10 mg of diazepam at two hours before elective surgery under general anesthesia did not significantly reduce the preoperative anxiety in comparison to a placebo. A study by Dyck et al in Toronto Hospital also reported that no difference of STAI anxiety level among the anxiolytic properties between diazepam 10 mg at 1-1.5 hour before operation, and placebo in the outpatient dilatation and curettage for therapeutic abortion[18]. These results were incompatible with Jakobsen et al [19], a double-blind study which showed that orally administered diazepam given early in the morning within 6 hours before operation resulted in significantly decreased preoperative discomfort in minor surgical operations such as hernia repair, treatment of varicose veins, excision of benign breast tumors, dilatation and curettage, laparoscopic sterilization, endoscopy and minor orthopedic operations. A randomized control study by Salami et al which reported that oral diazepam 5 mg was effective for VAS-P score pain reducing in the impacted mandibular third molar surgery[20]. The reason for this difference might be the difference of type of operation. Because, the LEEP patients had been diagnosed with intraepithelial cervical dysplasia or cervical cancer which had a higher concern than other types of surgery. Another explanation of non-significant difference between groups was the limitation of sample size, some trends of the reduction of anxiety score such as preoperative VAS-A score in the treatment group was seen, even its statistical significance weren't achieved. This could be explored in future studies with larger sample sizes. A higher dose of diazepam or another type of benzodiazepine such as triazolam, lorazepam or midazolam has been shown to reduce anxiety in other studies[15, 21-26]. However, it needs a longer period of postoperative observation due to the greater sedative effects of a higher dose. There were some studies reported that diazepam was less effective for anxiety reduction when compared with other anxiolytic drugs[17, 25]. However, diazepam has a lower cost and is more readily available than the other benzodiazepines in Thailand and other low- and middle-income countries. The impact of this study to clinical practice is that the administering preoperatively of 10 mg of oral diazepam is not effective for anxiety reduction and further studies which examine the proper dosage of diazepam for LEEP should be conducted. The other anxiolytic drugs such as non-benzodiazepine drug (nitrous oxide, melatonin, buspirone, barbiturates and beta-blocker) should be evaluated[27-31]. Multimodality medications using the combination of pharmacological and non-pharmacological is also interesting for future studies.

The strength of the present study was that it was a double-blind, placebo controlled, randomized trial study. However, the limitation was the context of the inpatient, intraoperative room and only in the LEEP which might affect the generalization of the application. Some variables such as education level and occupation were not included in this study and also the postoperative complication such as postoperative infection was not recorded. The limited sample size might influence the study outcome; therefore, the cost-effectiveness of diazepam needs further larger studies to determine its benefit in future clinical practice especially in the low resource setting.

Conclusion

Preoperative 10 mg oral diazepam at 1 hour before LEEP was not effective in the reduction of anxiety levels. The proper methods to reduce anxiety in this procedure still need further studies.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Efficacy of 10% Lidocaine Spray for Relief Postpartum Perineal Wound Pain: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the effectiveness of 10% lidocaine spray for reducing postpartum perineal wound pain.

Materials and Methods: Postpartum women who had spontaneous delivery with first- or second-degree perineal tears and received wound repair were randomly assigned into two groups. The intervention group received a 10% lidocaine spray, and the control group received a sterile water spray applied to the perineum every 6 hours until reaching 48 hours after delivery. The primary outcome was perineal wound pain using a 10-cm visual analog scale (VAS) 48 hours after delivery. Student t-test and generalized estimating equation (GEE) population-averaged model were used.

Results: Seventy-two women were randomly divided into two groups, 36 women in each group. Perineal wound pain at 24 and 48 hours in the lidocaine spray group was significantly lower than the control group (2.3 ± 0.2 vs 3.5 ± 0.2; mean difference 1.2; 95% confidence interval (CI) 0.4 to 2.0; p = 0.003) and (1.7 ± 0.2 vs 3.1 ± 1.6; mean difference 1.4; 95%CI 0.7 to 2.1; p < 0.001), respectively. Pain intensity in the lidocaine spray group was also significantly lower than the control group (mean difference = -0.4; 95%CI -0.6 to -0.1; p = 0.004). No serious adverse effects were observed in this study.

Conclusion: The 10% lidocaine spray was effective in the reduction of perineal wound pain after spontaneous delivery.

Keywords: perineal wound pain, pain control, lidocaine spray, postpartum.

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การศึกษาประสิทธิภาพของยาชาเฉพาะที่ชนิดพ่น 10% ลิโดเคน เปรียบเทียบกับยาหลอก ในการลดความเจ็บปวดบริเวณแผลฝีเย็บหลังคลอด: การทดลองแบบสุ่มที่มีการควบคุม

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บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพของยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10 ในการช่วยลดความเจ็บปวดบริเวณฝีเย็บในช่วงหลังคลอด*

วัสดุและวิธีการ*: สตรีหลังคลอดที่คลอดทางช่องคลอดที่มีการบาดเจ็บบริเวณฝีเย็บระดับหนึ่งหรือสองและได้รับการเย็บซ่อม จะถูกแบ่งออกเป็น 2 กลุ่มโดยการสุ่ม คือ กลุ่มที่ได้รับยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10 และกลุ่มที่ได้รับน้ำปลอดเชื้อเป็นกลุ่มควบคุม โดยทั้งสองกลุ่มจะได้รับการพ่นยาบริเวณฝีเย็บทุก 6 ชั่วโมงเป็นเวลา 48 ชั่วโมงหลังคลอดและผลลัพท์หลักเพื่อประเมินความเจ็บปวดบริเวณฝีเย็บ ที่ 48 ชั่วโมงหลังคลอด โดยใช้มาตรวัดความเจ็บปวดด้วยสายตา ขนาดความยาว 10 เซนติเมตร (visual analog scale) โดยใช้ student t-test และ generalized estimating equation (GEE) population-averaged model ในการคำนวน*

ผลการศึกษา*: สตรีหลังคลอด72 คนถูกสุ่มออกเป็นสองกลุ่ม กลุ่มละ 36 คน โดยพบว่ากลุ่มที่ได้รับยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10 มีความเจ็บปวดบริเวณฝีเย็บที่เวลา 24 และ 48 ชั่วโมงลดลงมากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (2.3 ± 0.2 vs 3.5 ± 0.2; mean difference 1.2; 95% confidence interval (CI) 0.4 to 2.0; p = 0.003) และ (1.7 ± 0.2 vs 3.1 ± 1.6; mean difference 1.4; 95%CI 0.7 to 2.1; p < 0.001) ตามลำดับ และระดับความรุนแรงของความเจ็บปวดในกลุ่มที่ได้รับยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10 น้อยกว่ากลุ่มควบคุม (mean difference = -0.4; 95%CI -0.6 to -0.1; p = 0.004) และไม่พบผลข้างเคียงรุนแรงจากงานวิจัยนี้*

สรุป*: ยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10 มีประสิทธิภาพในการช่วยลดความเจ็บปวดบริเวณแผลฝีเย็บหลังคลอดบุตรทางช่องคลอด*

คำสำคัญ*: แผลฝีเย็บ, การระงับปวด, ยาชาเฉพาะที่ชนิดพ่นลิโดเคนร้อยละ 10, สตรีหลังคลอด*

Introduction

Postpartum perineal pain commonly results from bruising, spontaneous tearing, or trauma such as episiotomy. Perineal pain is common among all postpartum women. The frequency and severity of the pain depend on the degree of perineal tearing[1]. Perineal pain may negatively affect mobility, interfere with breastfeeding, newborn care and self-care activities such as sleeping, resting, urination and bowel movements. It can impact sexual relationships and personal life, causing psychological and emotional problems during the puerperium[2], in which postpartum perineal pain levels are high over several postpartum day, and then declines over time[3]. Many methods have been proposed for postpartum perineal pain relief, for example nonpharmacological methods such as application of heat or cold therapy, warm sit baths, and music therapy, or pharmacological methods such as non-steroidal anti-inflammatory drugs (NSAIDs) and intravenous or epidural analgesia[4]. American College of Obstetricians and Gynecologists (ACOG) suggests the stepwise multimodal approach for management of pain after vaginal delivery, starting with NSAIDs or acetaminophen and using opioids only if necessary[5]. In contrast, Cochrane review does not recommend NSAIDs for breastfeeding women[6]. Moreover, adjunctive therapies such as topical agents for perineal pain, or ice and heat therapy can also support pain management, though evidence for their effectiveness is limited[5]. Harrison et al compared the aerosol formulations of 5% lignocaine, 2% cinchocaine and water spray in a single-dose, and reported that both local anesthetics offered significant relief from the perineal wound pain with the 5% lignocaine spray being more effective than 2% cinchocaine, but over time, the pain increased gradually after receiving local anesthetic spray[7]. Corkill et al reported the efficacy of lignocaine gel in reducing postpartum perineal pain. They found that the pain score in the lidocaine gel group was significantly lower than that of the control group at 48 hours after delivery, whereas the pain score was not significantly different at 24 hours after delivery. There was no difference in the consumption of oral analgesics between groups. This study suggested that lignocaine gel may be effective on the second postpartum day[8]. Abbas et al, who compared the effect of topical lidocaine-prilocaine cream versus rectal meloxicam suppository for relief of post-episiotomy pain. The results of the study showed no difference between groups using the visual analog scale, but the lidocaine-prilocaine group was reported lower scores at 12 hours and 5 days post-episiotomy[9].

Lidocaine is one of the most effective local anesthetic agents commonly used in medical procedures for reducing pain at mucosa or skin. Regarding the pharmacodynamics of lidocaine, it is voltage-gated sodium channel blocker, resulting in an inability to transmit signals of pain or stimulation[10].

Lidocaine spray is a convenient method and is easily used in clinical practice. Obstetric and gynecologic procedures, including first-trimester surgical abortion, intrauterine device insertion, endometrial sampling, and loop electrosurgical excision procedure (LEEP), have been investigated to determine the effectiveness of lidocaine spray in reducing pain[11].

Nowadays, the effectiveness of 10% lidocaine spray in alleviating the pain from perineal wound in the postpartum period remains uncertain due to insufficient evidence. Therefore, this study aimed to evaluate the efficacy of 10% lidocaine spray for relief post episiotomy pain.

Materials and Methods

This randomized controlled study was conducted between September 2023 and May 2024 at the Department of Obstetrics and Gynecology, Khon Kaen Hospital after approved by the Khon Kaen Hospital Institute Review Board in Human Research (KEF66015). The eligibility criteria were set as women aged 18 years old or above who underwent spontaneous vertex delivery with first- or second-degree perineal tear. The exclusion criteria were women who (a) had a postpartum hemorrhage; (b) underwent operative vaginal delivery by forceps or

vacuum extraction; (c) underwent manual placenta removal; (d) had multiple perineal lacerations; (e) had allergy to lidocaine; (f) had renal or hepatic diseases; (g) received epidural anesthesia; (h) had perineal infection (e.g., condyloma, chancroid, etc.); (i) had perineal wound hematoma; or (j) received lidocaine injection > 10 ml.

All eligible pregnant women were informed about the study by research assistants during their admission to the labor room. Written informed consent was individually obtained before the enrollment. Standard care was given to all participants during all stages of labor.

Lidocaine infiltration was performed on all women who were considered for the performance of restrictive episiotomy. Criteria for restrictive episiotomy were fetal distress, maternal conditions, history of severe perineal tearing, and larger fetal size. After vaginal delivery, physicians evaluated and sutured the perineal wound, and the severity of the perineal wound tear was checked. All cases received local infiltration anesthesia during perineal wound repair with 10 ml of 1% lidocaine HCL solution without adrenaline and plain catgut 2-0 was used to repair the perineal wound. Perineal repair was performed by an experienced physician or a nurse. After suturing the perineal wound, the participants were allocated randomly into two groups by computer-generated blocks of four and allocation concealment was done by using sealed opaque envelopes. Baseline characteristics were recorded.

The drug (10% lidocaine spray) and placebo (sterile water) which were identical in appearance were prepared in a pack by the pharmacist, under aseptic conditions. Each package was prepared and stored at room temperature. Lidocaine or placebo were applied by (spraying) five times/application onto the perineal wound for relief of pain after vaginal delivery every 6 hours by physician or trained nurse, with the first dose at 2 hours after delivery, with a total of 8 doses given to each participant. As the investigator and outcome assessor were two different people, the participants, the investigator, and the outcome assessor were therefore all blinded.

The intensity of the perineal pain was assessed using a 10-cm visual analog scale (VAS) at 2, 6, 12, 24, and 48 hours after delivery. The pain level on the VAS was identified with 0 representing "painless", and 10 representing "unbearable pain". Participants were asked to mark the point in the sitting position that they thought was related to the pain at that moment. When assessing mild to moderate pain, non-opioid analgesics should be considered first, with acetaminophen or ibuprofen being suitable options, as they are safe for breastfeeding mothers. Acetaminophen is typically recommended first. In this study, if the pain score was more than 4, the healthcare provider provided an analgesic drug (acetaminophen). If the level of pain was still not relieved, the healthcare provider provided NSAIDs (ibuprofen)[12]. Adverse effects were observed and recorded. If serious complications or side effects were presented, the drug was discontinued. Minor side effects such as nausea and vomiting were treated by symptomatic management. At 48 hours postpartum, participants were asked about their satisfaction with the application by using a 5-point Likert scale with the following options: completely satisfied, satisfied, no idea, dissatisfied and completely dissatisfied.

The sample size calculation was based on a pilot study with 20 women per group. The average pain score in the intervention group was 1.88 with a standard deviation (SD) of 1.21, whereas the pain score in the control group was 3.19 with SD of 1.79. With a power of 90%, an alpha error of 5%, and a dropout of 10%. The total participants were 72 women (36 women in each group). The primary outcome was the perineal wound pain score assessed by visual analog scale at 48 hours after delivery. The secondary outcomes were perineal wound pain at 6, 12, and 24 hours, side effects, additional analgesia and participant's satisfaction.

Data was analyzed using STATA version 17.0 based on an intention-to-treat analysis. The student t-test was used to analyze the continuous data. The Fisher's exact test was used to analyze categorical

data. The differences of pain reduction between the intervention group and the control group at different times studied were analyzed by the generalized estimating equation (GEE) population-averaged model. A p value of less than 0.05 was regarded as statistically significant.

Results

Between September 2023 and May 2024, 83 eligible women who underwent spontaneous vertex delivery with first- or second-degree perineal tear were enrolled into the study. Eleven of them were excluded from the study: two because of postpartum hemorrhage, eight because of multiple perineal wounds and one because of manual removal of placenta. Subsequently, a total of 72 eligible women were randomly assigned into two groups: 36 to the intervention group and 36 to the control group. There were no dropouts (Fig. 1).

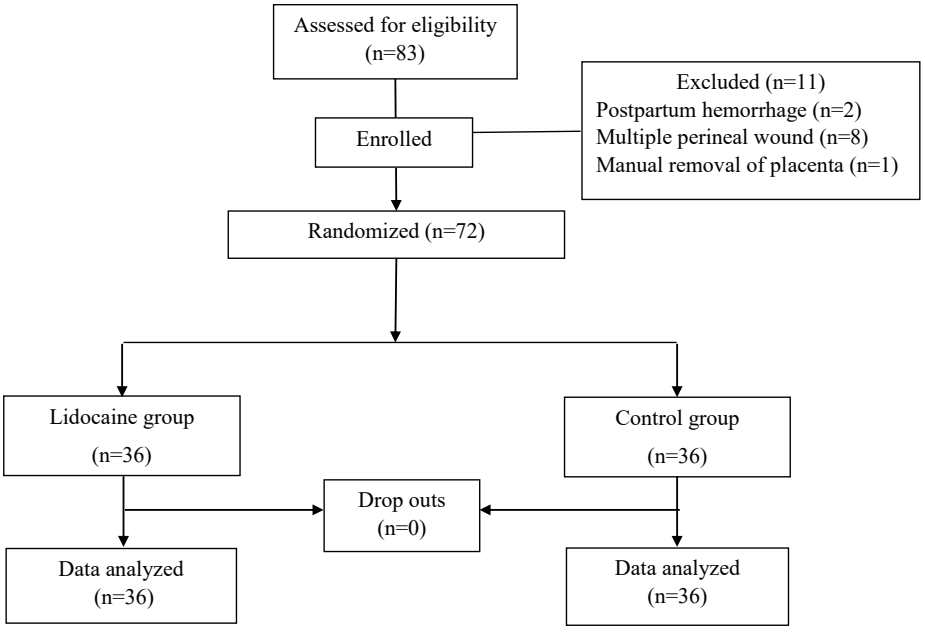

Fig. 1. Study flow diagram

Baseline characteristics (age, gestational age, body mass index, duration of each stage of labor, fetal birth weight, degree of vaginal tear, and duration of suture) were similar between groups, except for parity, in which the intervention group had a small proportion of nulliparous women compared to multiparous women than in the control group (Table 1).

Perineal wound pain at 48 hours of the intervention group (10% lidocaine spray) was significantly lower than that of the control group (1.72 ± 0.21 vs 3.16 ± 1.62; mean difference 1.44; 95%CI 0.75-2.14; p < 0.001) (Table 2).

Perineal wound pain at 24 hours of the intervention group was also significantly lower than that of the control group (2.33 ± 0.26 vs 3.56 ± 0.29; mean difference 1.23; 95%CI 0.45-2.01; p = 0.003). Perineal wound pain at 6 and 12 hours was not statistically significant between groups (3.63 ± 0.36 vs. 3.59 ± 0.37; mean difference 0.04; 95%CI -1.08-0.99; p = 0.934), (3.23 ± 0.3 vs. 3.72 ± 0.33; mean difference 0.49; 95%CI -0.4-1.39; p = 0.278), respectively (Table 3).

In the intervention group, the reduction of pain was significantly greater than that the control group (mean difference = -0.4; 95%CI -0.6 to -0.1; p = 0.004) as indicated by the GEE population-averaged model analysis (Table 4, Fig. 2).

Table 1. Baseline characteristics.

	Lidocaine group (n = 36)	Control group (n = 36)	p value
Maternal age (years), mean ± SD	27.17 ± 4.71	27.08 ± 6.35	0.950[a]
Body mass index (kg/m^2), mean ± SD	27.95 ± 4.71	27.91 ± 5.07	0.968[a]
Gestational age (weeks), mean ± SD	38.29 ± 1.99	38.40 ± 1.33	0.779[a]
Parity			0.173[b]
Nulliparous, n (%)	9 (25.0)	18 (50.0)	
Multiparous, n (%)	27 (75.0)	18 (50.0)	
Duration of first stage of labor (min), mean ± SD	556.25 ± 56.61	654.86 ± 66.35	0.262[a]
Duration of second stage of labor (min), mean ± SD	12.17 ± 1.61	13.94 ± 2.34	0.533[a]
Fetal birth weight (gm), mean ± SD	3,208.89 ± 435.30	2,981.94 ± 375.26	0.206[a]
Perineal wound, n (%)			0.527[b]
Episiotomy	31 (86.1)	29 (80.6)	
No episiotomy	5 (13.9)	7 (19.4)	
Degree of perineal tears			0.691[b]
First degree, n (%)	4 (11.1)	3 (8.3)	
Second degree, n (%)	32 (88.9)	33 (91.7)	
Duration of suture (min), mean ± SD	19.25 ± 9.46	17.83 ± 9.09	0.519[a]

[a] student t-test, [b] Fisher's extract test
SD: standard deviation

Table 2. Primary outcome.

Perineal wound pain	Lidocaine group (n = 36)	Control group (n = 36)	mean difference	95%CI	p value
At 48 hr. after delivery, mean ± SD	1.72 ± 0.21	3.16 ± 1.62	1.44	0.75 to 2.14	< 0.001[a]

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

Table 3. Secondary outcomes.

Perineal wound pain, mean ± SD	Lidocaine group (n = 36)	Control group (n = 36)	mean difference	95%CI	p value
2 hr. (baseline)	3.29 ± 0.39	3.34 ± 0.32	0.06	-0.95 to 1.06	0.912[a]
6 hr.	3.63 ± 0.36	3.59 ± 0.37	0.04	-1.08 to 0.99	0.934[a]
12 hr.	3.23 ± 0.30	3.72 ± 0.33	0.49	-0.40 to 1.39	0.278[a]
24 hr.	2.33 ± 0.26	3.56 ± 0.29	1.23	0.45 to 2.01	0.003[a]

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

Table 4. Comparison of perineal pain between the intervention and control groups.

Perineal wound pain, mean ± SD	Lidocaine group (n = 36)	Control group (n = 36)	mean difference	95%CI	p value
2 hr. (baseline)	3.29 ± 0.39	3.34 ± 0.32	0.06	-0.95 to 1.06	0.912[a]
6 hr.	3.63 ± 0.36	3.59 ± 0.37	0.04	-1.08 to 0.99	0.934[a]
12 hr.	3.23 ± 0.30	3.72 ± 0.33	0.49	-0.40 to 1.39	0.278[a]
24 hr.	2.33 ± 0.26	3.56 ± 0.29	1.23	0.45 to 2.01	0.003[a]
48 hr.	1.72±0.21	3.16±1.62	-0.4	-0.6 to -0.1	0.004[c]

[c] generalized estimating equation population-averaged model
SD: standard deviation, CI: confidence interval

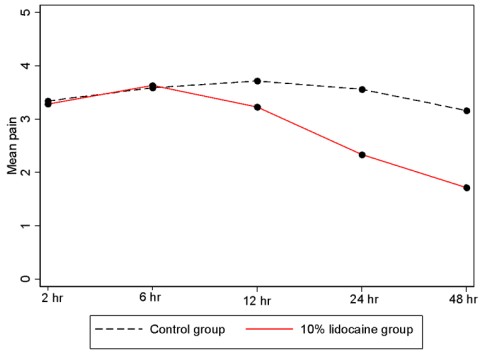

Fig. 1. Perineal wound pain during 48 hours after delivery.

Women in the intervention group were more completely satisfied with higher statistical significance than the women in the control group (75% vs 36.1%, p < 0.001). There was no significant difference in the need for additional analgesia with acetaminophen (16.7% vs 25 %, p = 0.384) or ibuprofen (27.8% vs 22.2%, p = 0.586) (Table 5).

Table 5. Additional analgesia and participant's satisfaction.

	Lidocaine group (n = 36)	Control group (n = 36)	p value
Post-episiotomy participant's satisfaction			
Completely satisfied, n (%)	27 (75.0)	13 (36.1)	0.001 [b]
Satisfied, n (%)	7 (19.4)	19 (52.8)	0.003 [b]
No idea, n (%)	2 (5.6)	4 (11.1)	0.394 [b]
Dissatisfied, n (%)	0	0	0
Completely dissatisfied, n (%)	0	0	0
The need for additional analgesia			
Ibuprofen (400), n (%)	10 (27.8)	8 (22.2)	0.586 [b]
Acetaminophen (500), n (%)	6 (16.7)	9 (25.0)	0.384 [b]

[b] Fisher's extract test. SD: standard deviation, CI: confidence interval

In this study, no adverse effects of the drug (burning sensation, bradycardia, hypotension, allergic reaction) or complications of the perineal wounds were found.

Discussion

In the current study, it was found that perineal wound pain at 48 hours in the 10% lidocaine spray group was significantly lower than that of the control. Additionally, this study found that the perineal wound pain at 24 hours of the 10% lidocaine spray group was also significantly lower than that of the control group. Moreover, the comparison of the reduction of pain between the intervention group and the control group using the GEE population-averaged model indicated that in the intervention group, pain reduction was more significant than that of the control group. Although the pain scores at 24 and 48 hours were less than 4 and the differences in scores were 1-2 points between groups, this current study found that there was a statistically significant difference; however, it may not be a clinically significant difference. Thus, further research on clinical factors, such as quality of breastfeeding, resting, urination, psychological and emotional conditions, and cost effectiveness, may be required. Even though the decrease in pain is only slight, it may increase the overall quality of life.

The results of this research were consistent with the findings of Harrison et al, which showed that lidocaine spray significantly reduced perineal pain. In addition, Corkill et al found that the efficacy of lignocaine gel in reducing postpartum perineal pain was more effective when administered continuously. Additionally, there was no difference in the consumption of oral analgesics between groups. These results aligned with our study, which showed that continuous local anesthesia at the perineal area reduced pain for 48 hours postpartum, without the differences of additional drugs used. However, our study found a reduction in pain during 24 hours after delivery. This may be attributed to differences in the current study, such as the higher concentration of the drug and the regular administration, which could prolong pain relief and provide a statistically significant reduction in pain during the 48 hours after delivery.

In comparison with the research of Chaichanalap et al [13], both studies included a variety of approaches in the management of postpartum pain. The research on music therapy demonstrated a significant reduction in immediate postpartum episiotomy pain, while our study on lidocaine spray showed effective pain relief compared to placebo for perineal wounds after vaginal delivery. Both methods were effective in reducing postpartum perineal pain but may serve different patient needs. Music therapy may be particularly beneficial for those seeking alternatives to medications, whereas lidocaine spray may be appropriate for patients needing immediate, localized pain relief. Harasai et al[14] studied the efficacy of a single dose of ibuprofen and acetaminophen compared to acetaminophen alone. The research demonstrated that the combination significantly reduces perineal pain after childbirth, similar to the current study, which showed effective pain relief for postpartum perineal wound pain. The combination of ibuprofen and acetaminophen offers analgesic effects through different mechanisms with ibuprofen as a non-steroidal anti-inflammatory drug (NSAID) and acetaminophen as an analgesic. In contrast, the lidocaine spray serves as a local anesthetic, directly targeting the site of the pain. Furthermore, Pattarasiriwong et al[15] found no significant differences in the efficacy of the pain reduction of acetaminophen/tramadol rectal suppositories compared to placebo in postpartum women following normal vaginal delivery. This contrasted with our study, which demonstrated that lidocaine spray provided effective pain relief for perineal wounds. This difference may suggest that while systemic analgesics such as acetaminophen and tramadol are beneficial in some contexts, they may not be as effective as local anesthetics in managing postpartum perineal pain.

Although the need for additional analgesia was not different, it remains consistent with the research of Corkill et al, which may be due to some women undergoing additional procedures after delivery such as postpartum sterilization in cases of multiparity. These women might require additional analgesics

(such as paracetamol or ibuprofen) to manage pain. In future studies, this confounding factor may need to be eliminated, or additional data may need to be collected for statistical analysis in this section. However, when comparing the satisfaction of using the drug and placebo, it was found that postpartum women were more completely satisfied with the use of the drug than placebo. Perineal wound pain reduction during the first few postpartum days may help postpartum women have a better quality of life, increase mobility, improve breastfeeding.

Although 10% lidocaine spray is a potential drug of choice for reducing the pain of perineal wounds during 48 hours postpartum, future research should focus on the other daily life activities, e.g. urination and defecation, lactation, psychosocial activities, other procedures after delivery, and the long-term side effects, and should also take into account the cost-effectiveness, operative vaginal delivery, third- or fourth-degree perineal tears, long-term outcomes and other confounding factors.

The key strengths of this study were that it was a randomized, double-blinded, placebo-controlled trial and it assessed the participant satisfaction. The limitations were the lack of analysis regarding the procedures such as postpartum tubal resection, which include the use of analgesics to control pain following the procedure.

The implication for practice was consideration of the application of 10% lidocaine for perineal pain relief during postpartum or its combination with other pain killers.

Conclusion

The 10% lidocaine spray effectively reduced perineal wound pain at 24 and, 48 hours after delivery without serious adverse effect.

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Potential conflicts of interest

The author declares no conflicts of interest.

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GYNAECOLOGY

Efficacy of Vitamin D on Vulvovaginal Atrophy in Menopausal Women: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of oral vitamin D supplementation in improving vulvovaginal atrophy in postmenopausal women over a 12-week period.

Materials and Methods: A double-blind randomized controlled trial involved 48 postmenopausal women with vulvovaginal atrophy. Participants were assigned to receive either 60,000 IU ergocalciferol weekly or placebo. Blinding was applied to both participants and healthcare providers. The primary outcome was vaginal maturation value (VMV) at 12 weeks. Secondary outcomes included VMV at 6 weeks, vaginal atrophy symptoms (VAS), modified vaginal health index (mVHI), vaginal atrophy score (VVA), vitamin D levels, and vaginal pH at 6 and 12 weeks.

Results: Baseline characteristics were not statistically significant between the two groups. In the intention-to-treat analysis, at 12 weeks after treatment, the vitamin D group exhibited significantly higher VMV compared with placebo (47.8 ± 25.24 and 27.4 ± 29.31, $p = 0.027$) and increased superficial cell count ($p = 0.036$). Furthermore, significant improvements in vaginal health index were observed in the vitamin D group at 6 and 12 weeks after treatment (VAS: $p = 0.030$ and $p < 0.001$, mVHI: $p < 0.001$ and $p < 0.001$, VVA: $p < 0.001$ and $p < 0.001$, vaginal pH: $p = 0.001$ and $p < 0.001$, vitamin D level: $p < 0.001$ and $p < 0.001$).

Conclusion: Vitamin D demonstrated superior efficacy over placebo in treating vulvovaginal atrophy in postmenopausal women. Those administered with vitamin D exhibited statistically significant enhancements in vaginal health index, including increased VMV, mVHI, and vitamin D levels, alongside decreased VAS, VVA, and vaginal pH. Therefore, vitamin D may be considered as an alternative treatment option for menopausal women with vulvovaginal atrophy, particularly in those with contraindications to hormone replacement therapy, vitamin D insufficiency, and vitamin D deficiency.

Keywords: postmenopausal women, vulvovaginal atrophy, vitamin D.

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ประสิทธิภาพของวิตามินดีในสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง

ชิโรซา เฮงพระธานี, สิรยา กิติโยดม

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของวิตามินดีแบบรับประทานในสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้งตลอดระยะเวลา 12 สัปดาห์*

วัสดุและวิธีการ: *ทำการศึกษาแบบสุ่ม (double-blind randomized controlled trial) ในกลุ่มอาสาสมัครสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง จำนวน 48 คน ณ แผนกผู้ป่วยนอกนรีเวชกรรมและคลินิกผู้สูงอายุ โรงพยาบาลมหาราชนครราชสีมา หลังจากถูกคัดออกตามเกณฑ์การคัดออกผู้เข้าร่วมการวิจัย อาสาสมัครจะถูกแบ่งเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ได้วิตามินดี 60,000 IU ต่อสัปดาห์และกลุ่มที่ได้รับยาหลอก โดยที่อาสาสมัคร แพทย์ พยาบาล ผู้ช่วยพยาบาลและนักเซลล์วิทยาจะไม่ทราบว่าใช้ยาชนิดใด ผลลัพธ์หลักคือค่า vaginal maturation value (VMV) ที่ 12 สัปดาห์หลังรับประทานวิตามินดี ผลลัพธ์อื่นๆที่สนใจ ได้แก่ VMV ที่ 6 สัปดาห์, vaginal atrophy symptoms (the most bothersome symptom) (VAS), modified vaginal health index (mVHI), vaginal atrophy score (VVA), vitamin D level และ vaginal pH ที่ 0, 6 และ 12 สัปดาห์หลังรับประทานยา*

ผลการศึกษา: *ข้อมูลพื้นฐานประชากรทั้งสองกลุ่มไม่แตกต่างกันทางสถิติ นำผลการทดลองที่ได้มาวิเคราะห์ความจำนงในการรักษา (intention to treat analysis) พบว่าที่ 12 สัปดาห์หลังรับประทานยา อาสาสมัครกลุ่มที่ได้วิตามินดีมี VMV มากกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติ (47.8 ± 25.24 และ 27.4 ± 29.3, p = 0.027) และ superficial cell มีจำนวนเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ (p = 0.036) นอกจากนี้ยังพบว่าอาสาสมัครกลุ่มที่ได้รับวิตามินดีมี vaginal health index ดีขึ้นที่ 6 และ 12 สัปดาห์ หลังรับประทานยาอย่างมีนัยสำคัญทางสถิติ (VAS: p = 0.030 and p < 0.001, mVHI: p < 0.001 and p < 0.001, VVA: p < 0.001 and p < 0.001, vaginal pH: p = 0.001 and p < 0.001, vitamin D level: p < 0.001 and p < 0.001).*

สรุป: *วิตามินดีมีประสิทธิภาพดีกว่ายาหลอกในการรักษาสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง สตรีวัยหมดระดูที่ได้รับวิตามินดีในการรักษาสภาวะช่องคลอดแห้งมี vaginal health index ดีขึ้นอย่างมีนัยสำคัญทางสถิติ ซึ่งได้แก่ VMV, mVHI และ vitamin D level มากขึ้น ในขณะเดียวกันค่า VAS, VVA และ vaginal pH มีค่าลดลง ดังนั้นวิตามินดีอาจเป็นทางเลือกหนึ่งในการรักษาสตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้งได้ โดยเฉพาะในกลุ่มสตรีที่มีข้อห้ามในการใช้ฮอร์โมนหรือมีภาวะพร่องหรือขาดวิตามินดี*

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Introduction

Vulvovaginal atrophy, a component of genitourinary syndrome, is characterized by the thinning and drying of the vaginal walls, resulting in reduced elasticity and diminished vaginal rugae[1]. Without treatment, the symptoms progressively worsen[2]. This condition is common in postmenopausal women due to declining estrogen and progesterone levels, leading to a decreased proportion of superficial and parabasal cells[3], vaginal wall thinning, lower lactic acid production, increased pH, and bacterial overgrowth, accompanied by reduced lactobacilli levels. These changes result in vaginal inflammation and infection.

The prevalence of vulvovaginal atrophy in the postmenopausal general population is 47%. However, vulvovaginal atrophy is underreported to healthcare professionals, with up to 63% of cases remaining unrecognized[4]. This leads to limited access to and delayed initiation of treatment, resulting in severe symptoms and a low quality of life. The standard treatment for vulvovaginal atrophy is hormonal replacement therapy. Additionally, non-hormonal therapies and alternative treatment options are available for individuals with contraindications to hormone therapy, such as lifestyle modifications, vaginal lubricants, vaginal moisturizers, vaginal laser therapy, and vitamin D supplementation.

Vitamin D also plays a role in influencing the development of vaginal epithelial cells through the vitamin D receptors – Ras homolog gene family – Ezrin pathway (VDR-RhoA-Ezrin pathway)[5]. Moreover, studies indicate that vitamin D deficiency in postmenopausal women reduces vaginal epithelial thickness[5], potentially contributing to vulvovaginal atrophy. Despite Thailand's location within the tropics and its abundant sunlight exposure throughout the year, the prevalence of vitamin D insufficiency is notably high, reaching 45.2%, with vitamin D deficiency reaching 5.7%[6]. The 2011 Endocrine Society Clinical Practice Guideline recommends supplementing 50,000 IU of vitamin D per week for individuals with a deficiency[7]. Previous studies[8-12] in the Middle East and South Asia examined vitamin D supplementation administered orally or vaginally for 8 weeks to 1 year, whereas another study[13] using a lower oral dosage for 12 weeks yielded inconsistent results. This study aimed to evaluate the effects of higher-dose oral vitamin D supplementation for 12 weeks at Maharat Nakhon Ratchasima Hospital, where vitamin D deficiency is prevalent and oral vitamin D is the sole available form. The outcomes of this study may provide benefits for the management of postmenopausal women suffering from vulvovaginal atrophy, potentially alleviating symptoms, promoting the development of vaginal epithelial cells, and ultimately improving their quality of life.

Materials and Methods

A double-blind randomized controlled trial was conducted involving 48 postmenopausal women with symptoms of vulvovaginal atrophy to evaluate the efficacy of 12-week oral vitamin D supplementation in improving their condition. The primary outcome measured was the vaginal maturation value (VMV) at 12 weeks after treatment. Secondary outcomes included VMV at 6 weeks, vaginal atrophy symptoms (the most bothersome symptom) (VAS), the modified vaginal health index (mVHI), vaginal atrophy score (VVA), levels of vitamin D, and vaginal pH at 6- and 12-weeks following treatment. The study protocol was approved by the Human Research Ethics Committee of Maharat Nakhon Ratchasima Hospital (MNRH IRB) with certificate number 083/2023 and registered with the Thai Clinical Trials Registry (TCTR) under certificate number TCTR20231107003.

Postmenopausal women experiencing symptoms of vulvovaginal atrophy were recruited from the outpatient department of gynecology and geriatric clinic at Maharat Nakhon Ratchasima Hospital between July 2023 and February 2024. All participants provided informed consent. The inclusion criteria comprised women with symptoms of vulvovaginal atrophy and postmenopausal status,

defined as the absence of menstruation for more than one year, a history of bilateral oophorectomy, or follicle-stimulating hormone (FSH) levels exceeding 40 IU/L. Exclusion criteria included a history of hormone or vitamin D use within the past 12 weeks, abnormal Pap smear results, active sexually transmitted diseases, abnormal uterine bleeding, severe medical conditions such as liver or renal failure, allergies to vitamin D or calcium, and a history of cancer or radiation therapy.

The sample size was determined based on a pilot study, where participants in the vitamin D group exhibited a mean VMV of 51.55 ± 28.78 at 12 weeks, while those in the placebo group had a mean VMV of 21.00 ± 28.26 at the same time point. The allocation ratio between the vitamin D and placebo groups was 1:1, with an α-error of 0.05 and a β value of 0.01. Additionally, a 25% allowance was made for a potential loss to follow-up, resulting in an adjusted total sample size of 48 participants.

Following the provision of information and informed consent, participants were randomly allocated into two groups: the vitamin D group and the placebo group, with 24 participants assigned to each group. This allocation was achieved through multiblock randomization generated by Microsoft Excel. Subsequently, the randomization sequence was blinded and revealed according to the predetermined order. Blinding procedures were implemented for participants, physicians, nurses, nurse assistants, cytologists, and statisticians involved in the trial throughout the study period. Both the ergocalciferol capsule (20,000 IU per capsule) and the placebo were identical in size, shape, and color. These capsules were repackaged in opaque packets and arranged in sets for 12 weeks, with the order randomized. All participants were instructed to consume either vitamin D or a placebo capsule every Monday, Wednesday, and Friday, accompanied by 1,000 mg of calcium carbonate orally with a meal every morning for 12 weeks. Furthermore, participants received guidance to implement lifestyle modifications and were instructed to refrain from consuming supplementary food, hormones, and herbal medicine throughout the study period.

All participants were provided with questionnaires and completed them independently. The questionnaires included questions about demographic characteristics and vaginal atrophy symptoms (the most bothersome symptoms) (VAS) [14]. Following the completion of the questionnaires, all participants underwent pelvic examinations conducted by second-year residents with one year of practice experience and similar levels of expertise. These examinations were conducted to evaluate vulvovaginal atrophy by assessing mVHI, VVA, vaginal pH, Pap smear, and VMV. Subsequently, blood samples (10 ml) were collected from all participants for vitamin D level analysis.

VMV was determined from cells collected from the upper one-third of the bilateral vaginal wall using the liquid-based technique (EASYPREP®). The collected cells were fixed in a preservation solution, smeared onto slides, and stained for examination by experienced cytologists. One hundred cells were counted and categorized into three types: superficial cells (S), intermediate cells (I), and parabasal cells (P). Subsequently, VMV was calculated using the formula VMV = (0 * P) + (0.5 * I) + (1 * S). VAS was determined through participants answering questionnaires themselves regarding vaginal atrophy symptoms, focusing on the most bothersome symptoms (VAS)[14]. The questionnaires inquired about the severity of symptoms, including vaginal dryness, vaginal itching, vaginal soreness, and dyspareunia. Scores ranged from 0 to 10, where a score of 0 indicated no symptoms, 1-3 indicated mild symptoms, 4-6 indicated moderate symptoms, and 7-10 indicated severe symptoms. mVHI and VVA were determined during the pelvic examination. The mVHI assessed various parameters including vaginal pH, moisture, rugosity, elasticity, length of the vagina, epithelium integrity, and vascularity. The VVA evaluated factors such as vaginal dryness, presence of rugae, vaginal color, existence of petechiae, and mucosal thinning. Vaginal pH was determined using

acid test strips (MQuant®), tested on the posterior upper one-third of the vaginal wall. Vitamin D levels were determined using the electrochemiluminescence immunoassay (ECLIA) technique. Each parameter was examined at 0, 6, and 12 weeks.

At each follow-up at 6 and 12 weeks, all participants were required to bring the remaining ergocalciferol or placebo to the physician for compliance verification and to ensure correct administration. Participants were reminded about proper medication intake, lifestyle modifications, and the importance of avoiding supplementary food, hormones, and herbal medicine throughout the study period. The physician inquired about any symptoms or side effects of the medication and encouraged participants to ask any questions they had or seek additional information.

All statistical analyses were conducted using STATA software. The intention to treat analysis method was employed to analyze the results of this study, which compared data between the vitamin D group and the placebo group. Descriptive statistics were employed to present the data. Independent t-tests were utilized for analyzing normally distributed continuous variables, Fisher's exact test for categorical data, and the Mann-Whitney U test for non-normally distributed continuous variables. Additionally, a repeated measures mixed model was applied for analyzing data with repeated measurements, including VMV, VAS, mVHI, VVA, vaginal pH, and vitamin D level. Statistical significance was considered when the p value was less than 0.05.

Results

Forty-nine postmenopausal women experiencing symptoms of vulvovaginal atrophy were enrolled in the outpatient department of gynecology and the geriatric clinic at Maharat Nakhon Ratchasima Hospital during the study period. One participant was excluded from the study due to an abnormal Pap smear, resulting in a total of forty-eight participants included in the analysis. These participants were then randomly assigned to two groups. By the 12th week, there were seven total losses to follow-up, comprising two from the vitamin D group and five from the placebo group. Thus, the total number of participants available for analysis was forty-one, with twenty-two in the vitamin D group and nineteen in the placebo group. (Fig. 1.)

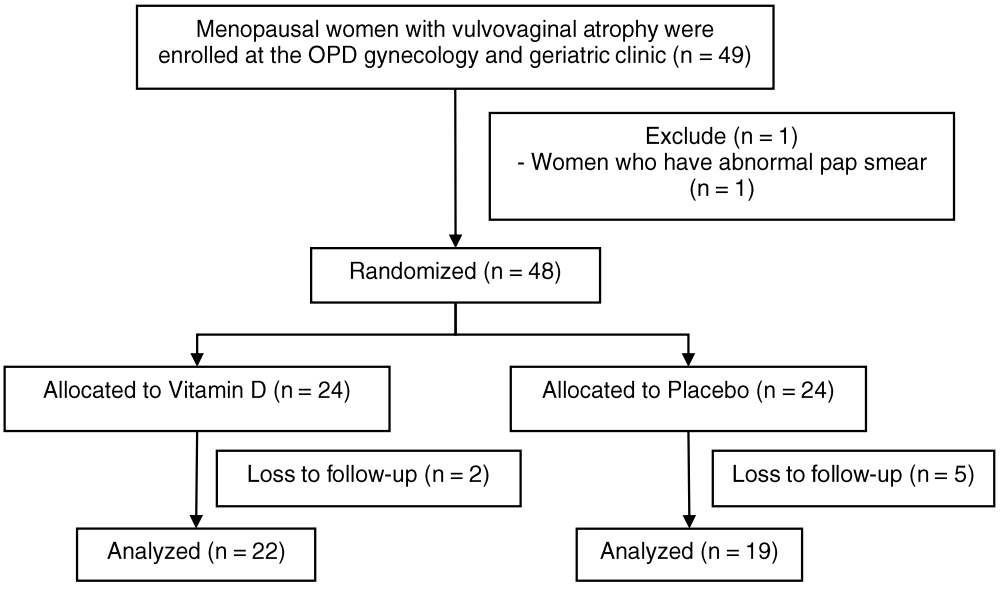

Fig. 1. The study flowchart.

All forty-one participants demonstrated good compliance with taking their assigned capsules. The demographic characteristics of both groups did not reveal significant differences (Table 1). The participants in this study ranged in age from 47 to 84 years. The majority of participants were obese (BMI ≥ 23 kg/m^2), with fifteen in the vitamin D group (68.19%) and ten in the placebo group (52.64%). Only one participant in the vitamin D group reported alcohol consumption, while none reported smoking. Risk factors for vulvovaginal atrophy (such as age at menopause, duration of menopause, active sexual activity, parity, and regular exercise) did not have statistically significant differences between the two groups. Furthermore, the vaginal health index of both groups, including VMV, VAS, mVHI, VVA, and vaginal pH, did not exhibit any significant differences. Most participants exhibited vitamin D insufficiency, and there was no significant difference in baseline vitamin D levels.

Table 1. Demographic characteristics.

Characteristic	Vitamin D (n = 22)	Placebo (n = 19)
Age (years)	65.45 ± 9.56	62.79 ± 7.39
Body Mass Index (kg/m^2)	25.07 ± 3.26	23.40 ± 4.29
Age at menopause (years)	48.27 ± 4.51	48.42 ± 6.39
Menopause duration (years)	17.18 ± 11.66	14.37 ± 9.73
Active sexual activity	9 (40.91)	11 (57.89)
Nulliparous	5 (22.73)	4 (21.05)
Having underlying medical diseases	15 (68.18)	13 (68.42)
Essential hypertension	8 (36.36)	8 (42.11)
Diabetes mellitus	4 (18.18)	2 (10.53)
Dyslipidemia	6 (27.27)	2 (10.53)
Regular exercise	7 (31.82)	6 (31.58)
History of intraabdominal surgery	12 (54.55)	6 (31.58)
Vaginal health measurement and Vitamin D level		
Vaginal maturation value (VMV)	43.64 ± 28.17	27.76 ± 29.44
Vaginal atrophy symptoms (VAS)	10.68 ± 2.30	9.05 ± 3.06
Modified vaginal health index (mVHI)	12.41 ± 1.99	13.21 ± 2.12
Vaginal atrophy score (VVA)	7.59 ± 1.53	6.421 ± 1.71
Vaginal pH	6.43 ± 0.70	6.18 ± 0.79
Vitamin D level (ng/ml)	25.68 ± 8.16	23.66 ± 7.98
Vitamin D deficiency (ng/ml)	16.43 ± 2.23	14.91 ± 5.31
	4 (18.18)	6 (31.58)
Vitamin D insufficiency (ng/ml)	23.79 ± 2.67	25.42 ± 2.85
	13 (59.09)	10 (52.63)
Vitamin D sufficiency (ng/ml)	38.00 ± 6.10	35.3 ± 4.26
	5 (22.73)	3 (15.79)

Data expressed as mean ± standard deviation or n (%)

In the 6th week, the VMV in the vitamin D group increased, though not reaching statistical significance. However, by the 12th week, the VMV in the vitamin D group (47.8 ± 25.24) showed a significant increase compared to the placebo group (p = 0.027). The mean difference (95%CI) was calculated to be 20.45 (2.14, 38.76) (Table 2, Fig. 2).

Table 2. Vaginal maturation value (VMV) between the vitamin D group and the placebo group at 0, 6, and 12 weeks.

Weeks	Vitamin D (n= 22) mean ± SD	Placebo (n= 19) mean ± SD	mean difference (95% confidence interval)	p value
0	43.6 ± 28.17	27.8 ± 29.44	15.87 (-1.58, 33.33)	0.075
6	48.1 ± 28.53	33.6 ± 32.64	14.52 (-3.16, 32.19)	0.107
12	47.8 ± 25.24	27.4 ± 29.31	20.45 (2.14, 38.76)	0.027*

Vaginal maturation value (VMV) = (0*Parabasal cell) + (0.5*Intermediate cell) + (1*Superficial cell)
SD: standard deviation

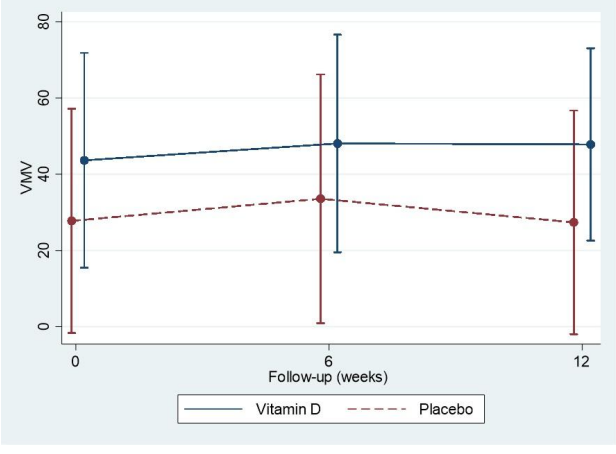

Fig. 2. Mean and standard deviation of vaginal maturation value by time, for the vitamin D and the placebo group.

Comparing the cytological findings of vaginal epithelial cells at the 6th and 12th weeks, it was observed that the vitamin D group exhibited a higher number of superficial cells compared to the placebo group. This increase was statistically significant at the 12th week (p = 0.036). However, no significant differences were observed for intermediate and parabasal cells at either the 6th or 12th week (Table 3).

When comparing other vaginal health indexes, it was found that the vitamin D group exhibited statistically significant improvement over the placebo group at both the 6th and 12th weeks. This improvement included an increase in mVHI and vitamin D levels, as well as decreases in VAS, VVA, and vaginal pH (Table 4, Fig. 3, 4). Moreover, this study did not find any instances of drug allergy or side effects associated with vitamin D, calcium carbonate, and placebo.

Table 3. Comparison of cytological findings between the vitamin D group and the placebo group at baseline, 6 and 12 weeks.

Cytological findings	Vitamin D (n= 22) median (P25, P75)	Placebo (n= 19) median (P25, P75)	p value Mann-Whitney U test
Superficial cell			
Baseline	15 (0,50)	5 (0,30)	0.209
6 weeks	25 (0,40)	5 (0,40)	0.262
12 weeks	30 (0,50)	0 (0,30)	0.036*
Intermediate cell			
Baseline	35 (20,60)	10 (0,40)	0.046
6 weeks	20 (20,60)	30 (0,60)	0.309
12 weeks	30 (20,56)	30 (0,60)	0.224
Parabasal cell			
Baseline	20 (10,80)	80 (10,100)	0.046*
6 weeks	20 (0,60)	35 (10,100)	0.161
12 weeks	25 (10,40)	70 (10,100)	0.076

Data expressed as median (P25, P75)

Table 4. Comparison of vaginal health measurement and vitamin D level between the vitamin D group and the placebo group at baseline, 6, and 12 weeks.

Vaginal health measurement and vitamin D level	Vitamin D (n = 22) mean ± SD	Placebo (n = 19) mean ± SD	mean difference (95% confidence interval)	p value
Vaginal atrophy symptoms (VAS)				
Baseline	10.7 ± 2.30	9.1 ± 3.06	1.63 (0.24, 3.01)	0.021*
6 weeks	2.4 ± 2.02	3.9 ± 2.41	-1.54 (-2.92, -0.15)	0.030*
12 weeks	0.6 ± 0.79	4.5 ± 2.50	-3.89 (-5.28, -2.50)	< 0.001*
Modified vaginal health index (mVHI)				
Baseline	12.4 ±1.99	13.2 ± 2.12	-0.80 (-1.91, 0.30)	0.156
6 weeks	17.5 ± 1.77	14.6 ± 1.92	2.88 (1.77, 3.98)	< 0.001*
12 weeks	18.4 ± 0.96	14.8 ± 1.92	3.57 (2.45, 4.68)	< 0.001*
Vaginal atrophy score (VVA)				
Baseline	7.6 ± 1.53	6.4 ± 1.71	1.17 (-0.15, 2.49)	0.082
6 weeks	3.5 ± 2.84	8.8 ± 3.17	-5.30 (-6.77, -3.82)	< 0.001*
12 weeks	1.3 ± 1.32	6.4 ± 4.17	-5.05 (-6.91, -3.19)	< 0.001*
Vaginal pH				
Baseline	6.4 ± 0.70	6.2 ± 0.79	0.25 (-0.14, 0.64)	0.216
6 weeks	5.8 ± 0.59	6.5 ± 0.65	-0.68 (-1.07, -0.29)	0.001*
12 weeks	5.4 ± 0.57	7.0 ± 0.53	-1.59 (-1.98, -1.20)	< 0.001*
Vitamin D level				
Baseline	25.7 ± 8.16	23.7 ± 7.98	2.02 (-3.78, 7.82)	0.495
6 weeks	43.7 ± 12.61	23.0 ± 6.82	20.70 (14.75, 26.66)	< 0.001*
12 weeks	45.9 ± 12.83	22.3 ± 9.08	23.62 (17.21, 30.03)	< 0.001*

SD: standard deviation

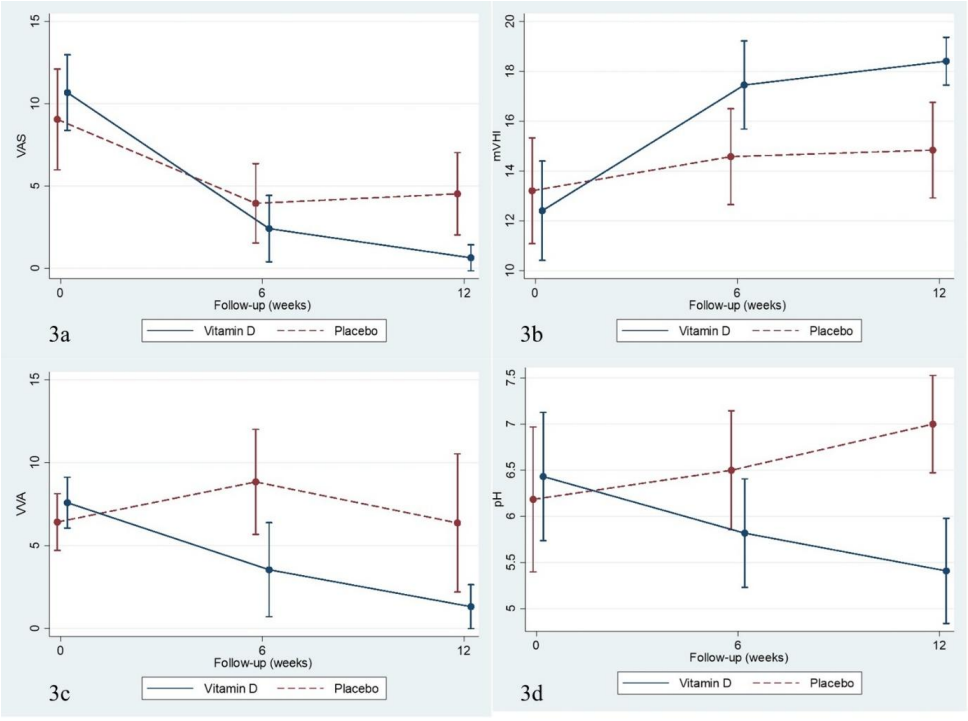

Fig. 3. Mean and standard deviation of (3a) vaginal atrophy symptoms, (3b) modified vaginal health index, (3c) vaginal atrophy score, and (3d) pH by time, for the vitamin D and the placebo group.

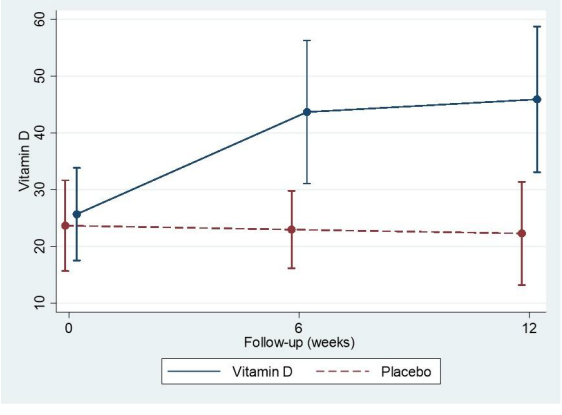

Fig. 4. Mean and standard deviation of vitamin D level by time, for the vitamin D and the placebo group.

Discussion

The administration of a weekly 60,000 IU ergocalciferol supplement for 12 weeks to postmenopausal women experiencing vulvovaginal atrophy resulted in statistically significant improvements in various aspects of the vaginal health index, including increased VMV, mVHI, and vitamin D levels, as well as decreased VAS, VVA, and vaginal pH when compared with a placebo.

At the 6th and 12th weeks, there was a noticeable

increase in the trend of superficial cells, leading to an overall increase in VMV. This could potentially be attributed to the influence of vitamin D on the VDR-RhoA-Ezrin pathway, which affects cell-to-cell junctions, subsequently promoting the proliferation of the vaginal epithelium and increasing superficial cells, and lowering vaginal pH[5].

Additionally, this study observed a significant reduction in VAS scores in the vitamin D group compared to the placebo group at the 6th and 12th weeks. This slightly decrease in the placebo group may be attributed to lifestyle modifications influenced by follow-up advice. Moreover, the VAS is a subjective measure of the most bothersome symptoms, and may also reflect a placebo effect, as noted by Mitchell et al[15]. The findings were consistent with Rad et al[11], which reported significant reductions in vaginal dryness, vaginal pH, and parabasal cell count, alongside increases in superficial cell count after 8 weeks of vitamin D administered via vaginal suppositories. They reported greater changes in parabasal cells, potentially due to the vaginal route facilitating the distribution and absorption of vitamin D into the vaginal epithelium through transcellular transport and receptor-mediated transcytosis[16, 17].

The previous study by Yildirim et al[8], using 20 IU calcitriol daily and calcium supplements in postmenopausal women for one year, reported a statistically significant increase in the percentage of superficial cells and a decrease in basal and parabasal cells in the vitamin D group. However, our study found no significant difference in parabasal cell counts. These may be attributed to our study administering ergocalciferol, an inactive form of vitamin D. While Yildirim et al[8], administered a longer duration of 1,25-dihydroxyvitamin D3 (calcitriol), an active form that can be utilized without undergoing the hydroxylation process in the liver and kidneys.

It's worth noting that, in this study, there was a statistically significant increase in VMV at the 12 weeks. However, Kamronrithisorn et al[13] revealed that the increase was non-statistically significant. This may be due to our study's inclusion of participants with vitamin D insufficiency and deficiency as well as our use of higher ergocalciferol doses, which may lead to a greater increase in VMV.

Furthermore, our study, in accordance with the findings of Bala et al[9] and Kaur et al[10], investigated participants with urogynecological conditions, who exhibited vitamin D deficiency. In both studies, participants were administered 60,000 IU cholecalciferol per week for 10 weeks, followed by maintenance doses every 3 months, resulting in significant increases in mVHI and vitamin D levels.

Moreover, a study by Riazi et al[12] found the appropriate duration for administering vitamin D to observe changes in vaginal health was between 8 to 10 weeks, except for vaginal dryness. This aligned with our findings demonstrated in Fig. 2 to 4. It can be observed that VMV and other vaginal health index improved during the first 0 to 6 weeks after vitamin D supplementation. Despite this, from weeks 6 to 12, the values showed slight improvement and tended to plateau.

Therefore, it may be concluded that vitamin D deficiency or insufficiency could be a contributing factor to worsening vaginal health index and may lead to symptoms of vulvovaginal atrophy. Treatment of vitamin D deficiency or insufficiency may help improve the vaginal health index, including increased VMV, mVHI, and vitamin D levels, and decreased VAS, VVA, and vaginal pH. The effectiveness may depend on the baseline vitamin D level, the form, dosage, duration, and route of vitamin D administration.

This study has several strengths. It was a double-blind study with blinding extended to volunteers, healthcare providers, cytologists, and statisticians. This comprehensive blinding approach helped to reduce bias in the study. Furthermore, the study evaluated the efficacy of vitamin D from multiple perspectives, including self-assessments by participants, physical examinations by physicians, blood tests to measuring vitamin D levels, and cytological evaluations, thereby enhancing its credibility and clarity.

This study also exhibits certain limitations.

Firstly, it was confined to a single center setting and solely investigates the oral administration of vitamin D. The sample size was relatively small, and subgroup analysis of baseline vitamin D levels was not feasible due to the limited number of participants. Future research should involve multicenter studies with larger cohorts to comprehensively explore the efficacy of vitamin D across different routes, dosages, and durations, as well as enable subgroup analysis of baseline vitamin D levels. Moreover, there is a need for clearer assessments of the quality of life and cost-effectiveness of vitamin D supplementation in postmenopausal women with vulvovaginal atrophy, especially for those with contraindications to hormone replacement therapy or those presenting with vitamin D insufficiency and deficiency, to improve patient care and quality of life.

Conclusion

Orally administering ergocalciferol at a dosage of 60,000 IU per week for 12 weeks resulted in a statistically significant improvement in the vaginal health, showing increased VMV, mVHI, and vitamin D levels, along with decreased VAS, VVA, and vaginal pH. These findings suggested that vitamin D could serve as a feasible alternative treatment for postmenopausal women with vulvovaginal atrophy, particularly beneficial for patients with contraindications to hormone replacement therapy or those presenting with vitamin D insufficiency and deficiency.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Patients' satisfaction with the Preoperative Informed Consent in Elective Gynecological Surgery in a Tertiary Hospital, BMA

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ABSTRACT

Objectives: This study aimed to evaluate patients' satisfaction with the preoperative informed consent process in elective gynecological surgery.

Materials and Methods: This cross-sectional study was conducted at Charoenkrung Pracharak Hospital, Bangkok, Thailand, from October 2023 to May 2024. Personal data and satisfaction with the preoperative informed consent process were collected on the second postoperative day. The Thai version of the decisional satisfaction scale (DSS) was used to measure satisfaction and the informed consent process questionnaire was used to assess knowledge of surgery and perception of informed consent process. Bivariate associations between highly satisfied and not highly satisfied groups were tested using Fisher's exact test.

Results: A total of 178 participants were enrolled, with a mean age of 42.48 years. Most participants agreed or strongly agreed with the statements on the DSS, a mean total score was 27.87, indicating high overall satisfaction. One hundred and thirty-five patients (75.8%) were highly satisfied with the informed consent process. There were several factors with significant differences between the highly satisfied group and not highly satisfied group. These included being informed about the consequences of not undergoing the procedure, knowing enough about the procedure to explain it, being informed about the reasons for prolonged urine catheterization and being given the opportunity to refuse the procedure.

Conclusion: This study highlighted the critical role of an effective informed consent process in elective gynecological surgery. High patient satisfaction was achieved when communication and patient participation were prioritized. Future research should explore these dynamics in different settings and diverse populations.

Keywords: patients satisfaction, decisional satisfaction scale, informed-consent process, elective gynecological surgery.

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ความพึงพอใจของผู้ป่วยต่อการขอความยินยอมก่อนการผ่าตัดทางนรีเวชแบบไม่ฉุกเฉิน ในโรงพยาบาลตติยภูมิสังกัดกรุงเทพมหานคร

ทศพร ช่วยสถิตย์, อภิชญา ปรัชญาชัยพิมล, จิรพร เหลืองเมตตากุล

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินความพึงพอใจของผู้ป่วยต่อการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดและตรวจสอบความสัมพันธ์ระหว่างปัจจัยส่วนบุคคล ปัจจัยการรักษา และกระบวนการให้ข้อมูลและขอความยินยอมในการผ่าตัดทางนรีเวชแบบไม่ฉุกเฉิน*

วัสดุและวิธีการ*: การศึกษานี้เป็นการศึกษาแบบภาคตัดขวางที่ดำเนินการในโรงพยาบาลเจริญกรุงประชารักษ์ กรุงเทพมหานคร ประเทศไทย ระหว่างเดือนตุลาคม พ.ศ. 2566 ถึง พฤษภาคม พ.ศ. 2567 โดยข้อมูลส่วนบุคคลและความพึงพอใจต่อกระบวนการให้ข้อมูลและขอความยินยอมก่อนผ่าตัดของผู้เข้าร่วมวิจัยถูกเก็บรวบรวมในวันที่ 2 หลังการผ่าตัด โดยใช้แบบประเมินความพึงพอใจของผู้ป่วยต่อการให้ข้อมูลในการขอความยินยอมก่อนการผ่าตัดทางนรีเวชแบบไม่ฉุกเฉิน และแบบสอบถามกระบวนการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดฉบับภาษาไทย ซึ่งความพึงพอใจถูกวัดด้วยแบบสอบถามที่ประกอบด้วยข้อคำถาม 6 ข้อ ความรู้เกี่ยวกับการผ่าตัดและการรับรู้ถึงกระบวนการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดถูกวัดด้วยแบบสอบถามกระบวนการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดจำนวน 21 ข้อคำถาม ความสัมพันธ์ระหว่างกลุ่มที่พึงพอใจสูงและไม่ได้พึงพอใจสูงถูกทดสอบโดยใช้ Fisher exact test*

ผลการศึกษา*: ผู้เข้าร่วมการศึกษา 178 คน อายุเฉลี่ย 42.48 ปี โดยส่วนใหญ่เห็นด้วยหรือเห็นด้วยอย่างยิ่งกับข้อความในแบบวัดความพึงพอใจในการตัดสินใจ (Decisional Satisfaction Scale: DSS) คะแนนรวมเฉลี่ยคือ 27.87 บ่งชี้ว่ามีความพึงพอใจโดยรวมสูง ผู้ป่วย 135 คน (ร้อยละ 75.8) มีความพึงพอใจสูงต่อกระบวนการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดทางนรีเวช ซึ่งปัจจัยที่ส่งผลต่อความพึงพอใจอย่างมีนัยสำคัญ ได้แก่ การได้รับข้อมูลเกี่ยวกับผลกระทบที่อาจเกิดขึ้นหากไม่ทำการผ่าตัด การเข้าใจขั้นตอนการผ่าตัดจนสามารถอธิบายให้ผู้อื่นฟังได้ การได้รับข้อมูลเกี่ยวกับเหตุผลของการใส่สายสวนปัสสาวะเป็นเวลานานหากจำเป็น และการได้รับโอกาสในการปฏิเสธการผ่าตัด*

สรุป*: การศึกษานี้เน้นย้ำถึงบทบาทสำคัญของกระบวนการให้ข้อมูลและขอความยินยอมที่มีประสิทธิภาพก่อนการผ่าตัดทางนรีเวชแบบไม่ฉุกเฉิน โดยแสดงให้เห็นว่าผู้ป่วยมีความพึงพอใจสูงเมื่อมีการให้ความสำคัญกับการสื่อสารและการมีส่วนร่วมของผู้ป่วย งานวิจัยในอนาคตสามารถต่อยอดโดยมุ่งสำรวจในบริบทและกลุ่มประชากรที่หลากหลายขึ้นเพื่อยืนยันผลและปรับปรุงกระบวนการให้ข้อมูลและขอความยินยอมก่อนการผ่าตัดในสภาพแวดล้อมต่างๆ*

คำสำคัญ*: ความพึงพอใจของผู้ป่วย, แบบวัดความพึงพอใจในการตัดสินใจ, กระบวนการให้ข้อมูลและขอความยินยอมก่อนผ่าตัด, การผ่าตัดทางนรีเวชแบบไม่ฉุกเฉิน*

Introduction

The informed consent process is a long-standing fundamental principle of the practice of medicine, mandating that doctors must get patients' permission before doing any procedure. It means keeping patients in the loop about what exactly is going on, informing them of their diagnosis and treatment options, and letting them choose whether to continue. Patients should be well educated with high-quality evidence-based information on the disease and its severity, management options (both likelihood of benefit and harm), both medical and surgery risks. Patients should also be educated on treatment results and the potential implications of declining recommended therapy[1].

Informed consent is an important part of the doctor–patient relationship that helps to improve patient satisfaction[2-5], a key healthcare quality indicator[6]. All stages, such as preoperative, intraoperative and postoperative phases, must provide accurate and sufficient information about treatment options along with obtaining written consent. Levels of patient satisfaction with informed consent differ between countries ranging from 49% to 95%[7-10] in Pakistan, Israel, Netherlands, and Switzerland. However, some African nations like Rwanda, Botswana, Eritrea and Ethiopia have lower figures ranging from 36.9% to 67.4%[11-14]. Satisfied patients are more likely to adhere to treatment plans and keep appointments, they also show lower readmission rates and the hospitals with higher scores get significant improvement of postoperative mortality rates[15].

Studies showed that patients' satisfaction with preoperative care is dependent on various factors, such as the information given by doctors about the disease and preoperative details, the standardized consent forms, previous experiences of the disease or surgery, duration spent on information and consent, doctor-patient relationship[16-25]. Therefore, informed consent should not be a mere formality but an opportunity for patients to clarify any ambiguities with their physicians.

Under this hospital's Obstetrics and Gynecology Department, Charoenkrung Pracharak, pre-operative information is provided to all patients in both non-emergency and emergency cases. For non-emergency surgeries, once a diagnosis is finalized, they are informed at the outpatient department about their condition, surgical treatment plans and medication. The attending physician explains in detail the benefits and complications that are likely to come up during the whole process. However, the consent process has not yet been evaluated for patient satisfaction regarding understanding, completeness of information, addressing questions before deciding to undergo surgery, and enabling informed, independent decisions.

Therefore, the research team conducted this cross-sectional study to evaluate patient satisfaction with the information provision and consent process before gynecological surgery in a tertiary hospital. The study also aimed to assess patients' understanding of preoperative information. The findings will be used to improve the preoperative information process, enhancing patient satisfaction and safety, and ensuring safe and effective care.

Materials and Methods

This was a cross-sectional study conducted at Charoenkrung Pracharak Hospital in Bangkok, Thailand between October 2023 to May 2024. The study protocol was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (R003hc/66_EXP). Sample size in this study was based on Glaiza S de Guzman's 2022 study[25] that reported 70.7% prevalence of highly satisfied with informed consent process. The total sample size after accounting for an estimated 10% data loss was 178. Participants aged between twenty and sixty-five years, scheduled for elective major gynecological surgery in the hospital, and able to communicate in Thai were included.

Study participants were recruited from patients attending the Gynecology outpatient department and

Minimally Invasive Surgery Center. Members of the research team introduced themselves to patients when they came for their appointment leaving adequate time for them to make an informed decision about participation. Further opportunities were also given by researchers to allow patients to ask more questions regarding the research objectives. Patients were provided with additional documents concerning the research and were told why it won't affect their medical care if they chose to participate voluntarily. For those who declined, nothing changed in terms of their regular medical treatment procedure.

During the elective gynecological surgery conducted at Charoenkrung Pracharak Hospital, questionnaires were completed by patients. Eligible individuals were volunteers who were between the ages of 20 and 65 years old, could read and write in Thai language and fulfilled the inclusion criteria.

The process of data collection involved:

1. The outpatients department's doctors also gave some information about the disease and treatment options to these patients before their surgeries were scheduled for surgical management. For example, if surgery was intended for treatment, disease details, treatment choices, benefits, risks, operation procedures performed during surgery such as potential complications that may arise during surgery; additional operations or procedures which be immediately required after the complication occurred; among others as well as possible further surgeries which may be needed soon afterwards were all provided to them. This information was given in a series of steps:

- Initial information was provided by gynecologists at the outpatient department.

- Minimally Invasive Surgery Center's medical staff offered advice to those who would choose laparoscopic surgery.

- The attending gynecologists at the gynecology ward or the treating surgeon provided information on the day of admission before surgery.

2. The researchers selected volunteers through random sampling from patients undergoing elective gynecological surgery at Charoenkrung Pracharak Hospital. The selection included patients in all the gynecologic wards.

3. On the second day postoperatively using a three-part questionnaire data will be collected:

Part 1: Participants' personal information

Part 2: Decisional satisfaction scale (DSS) questionnaire developed by Sung et al[26]. There were a total of 6 items rated on a five-point Likert scale ("strongly disagree" to "strongly agree"). The instrument demonstrated high reliability, with a Cronbach's alpha of 0.95. Permission was obtained prior to its use, and the questionnaire was adapted. Content validity was then assessed by three experts (Obstetrics and Gynecology faculty members), and revisions were made based on their feedback. Subsequently, the instrument was tested for reliability on a group of 30 patients with characteristics similar to the study sample. Using Cronbach's alpha coefficient, the reliability score was 0.9. After confirming its reliability, the instrument was applied to the actual study sample. The DSS score is between 6 and 30, where scores of 26-30 are classified as highly satisfied while a score below that range classifies as not highly satisfied.

Part 3: This part of the questionnaire was to evaluate the informed consent process before elective gynecological surgery, from a patient's perspective. Its mechanism was built on a method of Hallock et al[21]. Twenty-one yes/no questions. After revisions based on the feedback of three independent obstetrician/gynecology experts, we updated this adapted questionnaire and tested its content validity. The pilot test was conducted with 30 patients with similar characteristics to the sample of the study, and a value superior or equal than 0.8 in Cronbach's alpha coefficient used as good reliability previous criteria for using at this actual sample.

The questionnaires were self-printed using identification codes, instead of names. All 3 sections

of the questionnaire were prepared by researchers, and medical records review was done to standardize data completeness.

The primary outcome was the prevalence of patient satisfaction with the informed consent process prior to elective gynecological surgery. The secondary outcomes were the relationships between personal factors, treatment factors, and the informed consent process with patient satisfaction before elective gynecological surgery.

All data were analyzed using SPSS software (version 26), with statistical significance set at $p < 0.05$. Descriptive statistics were used to summarize the data, presented as numbers, percentages, means, and standard deviations.

The chi-square test or Fisher Exact test was employed to compare proportions of categorical data (e.g., sex, underlying disease, diagnosis, complication) between the highly satisfied and not highly satisfied groups. For continuous data (e.g., age, body mass index, information time), the independent t-test was used if the data were normally distributed; otherwise, the Mann-Whitney U test was applied.

Results

Between October 2023 and May 2024, 212 participants were recruited for the study. Of these, 19 participants declined enrollment, and 15 were excluded based on the exclusion criteria: four due to mental health problems and eleven due to illiteracy in Thai. Consequently, the final number of participants was 178. The mean age of the respondents was 42.48 ± 9.68 years. The majority held a bachelor's degree or higher (51.1%), were married (64.6%), had no underlying diseases (82.6%), and were self-employed (37.1%). A history of previous surgery was reported by 32.6% of participants. The mean information time was 15.01 ± 7.09 minutes. The most common diagnosed condition was uterine disease (72.5%), with laparoscopic procedures used in 118 cases (66.3%). There were three cases of complications (1.7%): one bladder injury and two bowel injuries. Table 1 summarizes the demographic data and clinical characteristics of participants.

Table 1. Demographic data and clinical characteristics of participants (n = 178).

Characteristics	Total (n = 178)	
	n	%
Age (years)		
20-34	39	21.9%
35-49	101	56.7%
50-65	38	21.3%
mean ± SD	42.48 ± 9.68	
Race		
Thai	176	98.9%
not Thai	2	1.1%
BMI (kg/m^2)		
< 18.5	11	6.2%
18.5-22.9	76	42.7%
23.0-24.9	25	14.0%
25.0-29.9	41	23.0%
≥ 30	25	14.0%
mean ± SD	24.15 ± 4.77	
Income (Baht)		
< 10,000	31	17.4%
10,000-20,000	77	43.3%
20,001-30,000	29	16.3%
> 30,000	41	23.0%

Table 1. Demographic data and clinical characteristics of participants (n = 178). (Cont.)

Characteristics	Total (n = 178)	
	n	%
Education		
Secondary school and below	30	16.9%
High school	37	20.8%
Vocational education	20	11.2%
Bachelor's degree and above	91	51.1%
Marital		
Single	59	33.1%
Married	115	64.6%
Divorce	4	2.2%
Occupation		
Government Employee	21	11.8%
Self-employed	66	37.1%
company employee	54	30.3%
Housewife/Unemployed	37	20.8%
Underlying Disease		
Yes	31	17.4%
No	147	82.6%
Previous gynecological disease	9	5.1%
Prior Surgery	58	32.6%
Information time (min)		
< 10	15	8.4%
10-15	113	63.5%
15-30	50	28.1%
mean ± SD	15.01 ± 7.09	
Information provider		
Staff	129	72.5%
Resident	49	27.5%
Diagnosis		
Uterus	129	72.5%
Ovary	32	18.0%
Fallopian tube	17	9.5%
Approach		
Laparoscopy	118	66.3%
Exploratory	54	30.3%
Vaginal hysterectomy	6	3.4%
Procedure		
Hysterectomy	109	61.2%
Myomectomy	15	8.4%
Adnexal surgery	54	30.4%
Complications		
Yes	3	1.7%
No	175	98.3%
bladder injury	1	0.6%
bowel injury	2	1.1%

SD: standard deviation, BMI: body mass index

Most participants agreed or strongly agreed with the statements on the decisional satisfaction scale (DSS), resulting in a mean total score of 27.87 ± 2.77, indicating high overall satisfaction. Table 2 presents the respondents' scores on the DSS, while Table 3 provides a summary of overall satisfaction with the decision scale.

Table 2. Decisional satisfaction scale (n = 178).

Parameters	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	mean ± SD
1. I am satisfied that I was adequately informed about my disease and choice of treatment.		1 0.6%	2 1.1%	48 27.0%	127 71.3%	4.69 ± 0.52
2. I am satisfied that I was adequately informed about appropriate postoperative care.		1 0.6%	2 1.1%	55 30.9%	120 67.4%	4.65 ± 0.53
3. I am satisfied that I was adequately informed about treatment guidelines and potential complications that may occur.	1 0.6%	1 0.6%	5 2.8%	54 30.3%	117 65.7%	4.60 ± 0.63
4. I am satisfied that the doctor provided an opportunity for questions and respected my decision-making.		1 0.6%	2 1.1%	45 25.3%	130 73.0%	4.71 ± 0.51
5. I am satisfied with the amount of time I had to make decisions before the surgery.		1 0.6%	7 3.9%	60 33.7%	110 61.8%	4.57 ± 0.60
6. I am satisfied with my decision		1 0.6%	2 1.1%	55 30.9%	120 67.4%	4.65 ± 0.53
Total scores (5-30)						**27.87 ± 2.77**

Table 3. Summary of overall satisfaction with decision scale.

Score Range, Interpretation	n	%
Highly satisfied ≥ 26	135	75.8%
Not highly satisfied 5-25	43	24.2%

A total of 135 patients (75.8%) reported high satisfaction with the consent process prior to elective gynecological surgery. The key factors significantly influencing their satisfaction included being informed about the possible consequences of not undergoing the procedure, understanding the procedure well enough to explain it to others, being informed about the reasons for prolonged urine catheterization if necessary, and being given the opportunity to refuse the procedure. These findings are detailed in Table 4.

There was no significant correlation between patient satisfaction and the variables of age (p = 0.465), educational background (p = 0.320), civil status (p = 0.281), occupation (p = 0.680), prior gynecological disease (p = 0.509), history of surgery (p = 0.706), information time (p = 0.680), information provider (p = 0.648), procedure type (p = 0.509), and complications (p = 1.000) (Table 5).

Table 4. Responses to the informed consent questionnaire comparing patients who were highly satisfied to those who were not highly satisfied. (n = 178)

Questions	Total (n = 178)		Patients' satisfaction				p value
			Highly (n = 135)		Not highly (n = 43)		
	n	%	n	%	n	%	
1. Had you been given an explanation of the disease, including its nature and how it develops?	176	98.9%	134	99.3%	42	97.7%	0.426
2. Was the procedure explained to you?	176	98.9%	133	98.5%	43	100%	1.000
3. Were you informed about possible consequences of not having the procedure?	170	95.5%	132	97.8%	38	88.4%	0.010*
4. Were you informed about the alternatives to the procedure?	165	92.7%	127	94.1%	38	88.4%	0.211
5. Do you know enough about the procedure that you could basically explain to another person how it would occur?	175	98.3%	135	100%	40	93.0%	0.013*
6. Were you informed of the risks of the procedure?	177	99.4%	135	100%	42	97.7%	0.242
7. Do you understand the risks of the procedure?	176	98.9%	135	100%	41	95.3%	0.057
8. Were you informed of the benefits of the procedure?	178	100%	135	100%	43	100%	-
9. Do you understand the benefits of the procedure?	178	100%	135	100%	43	100%	-
10. Do you know the success rate of the procedure?	162	91.0%	123	91.1%	39	90.7%	0.934
11. Were you informed of the possibility of common complications from the procedure?	171	96.1%	131	97.0%	40	93.0%	0.238
12. Were you informed of the most severe possibility of a life-threatening complication from the procedure?	148	83.1%	115	85.2%	33	76.7%	0.198
13. Were you informed of the recovery period after procedure?	176	98.9%	133	98.5%	43	100%	1.000
14. Do you know about the duration of the hospital recovery period?	172	96.6%	131	97.0%	41	95.3%	0.633
15. Do you know about post-operative care instructions?	164	92.1%	124	91.9%	40	93.0%	0.804
16. Were you informed about the reason to prolong urine catheter if needed?	125	70.2%	100	74.1%	25	58.1%	0.047*
17. Do you feel that adequate time was spent providing you with all the information you need?	176	98.9%	134	99.3%	42	97.7%	0.426
18. Were you given the opportunity to ask questions before making the decision?	178	100%	135	100%	43	100%	-
19. Were you given the opportunity to refuse the procedure?	152	85.4%	121	89.6%	31	72.1%	0.005*
20. Were relatives invited to be informed about the procedure? (As per patient's preference)	156	87.6%	121	89.6%	35	81.4%	0.153
21. Do you get all the information you need to make a good decision about the procedure?	178	100%	135	100%	43	100%	-

p values from chi-square test or Fisher's exact test, * significant at p value < 0.05

Table 5. Demographic and clinical characteristics of participants, and the association between these characteristics and patients' satisfaction (n = 178).

Characteristics	Patients' satisfaction				p value
	Highly (n = 135)		Not highly (n = 43)		
	n	%	n	%	
Age (years)					0.465
20-34	31	23.0%	8	18.6%	
35-49	78	57.8%	23	53.5%	
50-65	26	19.3%	12	27.9%	
mean ± SD	41.94 ± 9.57		44.16 ± 9.93		0.191
Race					1.000
Thai	133	98.5%	43	100%	
Not Thai	2	1.5%	0	0%	
BMI (kg/m^2)					0.599
< 18.5	9	6.7%	2	4.7%	
18.5-22.9	54	40.0%	22	51.2%	
23.0-24.9	18	13.3%	7	16.3%	
25.0-29.9	33	24.4%	8	18.6%	
≥ 30	21	15.6%	4	9.3%	
mean ± SD	24.37 ± 4.91		23.47 ± 4.28		0.272
Income (Baht)					0.778
< 10,000	24	17.8%	7	16.3%	
10,000-20,000	57	42.2%	20	46.5%	
20,001-30,000	24	17.8%	5	11.6%	
> 30,000	30	22.2%	11	25.6%	
Education					0.320
Secondary school and below	20	14.8%	10	23.3%	
High school	26	19.3%	11	25.6%	
Vocational education	15	11.1%	5	11.6%	
Bachelor's degree and above	74	54.8%	17	39.5%	
Marital					0.281
Single	43	31.9%	16	37.2%	
Married	90	66.7%	25	58.1%	
Divorce	2	1.5%	2	4.7%	
Occupation					0.680
Government Employee	15	11.1%	6	14.0%	
Self-employed	48	35.6%	18	41.9%	
Company employee	44	32.6%	10	23.3%	
Housewife/Unemployed	28	20.7%	9	20.9%	
Underlying Disease					0.105
Yes	115	85.2%	32	74.4%	
No	20	14.8%	32	74.4%	
Previous gynecological disease	6	4.4%	3	7.0%	0.509
Prior Surgery	45	33.3%	13	30.2%	0.706
Information time (min)					0.680
< 10	10	7.4%	5	11.6%	
10-15	87	64.4%	26	60.5%	
15-30	38	28.1%	12	27.9%	
mean ± SD	15.13 ± 7.08		14.65 ± 7.19		0.677

Table 5. Demographic and clinical characteristics of participants, and the association between these characteristics and patients' satisfaction (n = 178). (Cont.)

Characteristics	Patients' satisfaction				p value
	Highly (n = 135)		Not highly (n = 43)		
	n	%	n	%	
Information provider					0.648
Staff	99	73.3%	30	69.8%	
Resident	36	26.7%	13	30.2%	
Diagnosis					0.720
Uterus	96	71.1%	33	76.7%	
Ovary	26	19.3%	6	14.0%	
Fallopian tube	13	9.6%	4	9.3%	
Approach					0.522
Laparoscopy	90	66.7%	28	65.1%	
Exploratory	41	30.4%	13	30.2%	
Vaginal hysterectomy	4	3.0%	2	4.7%	
Procedure					0.509
Hysterectomy	80	59.3%	29	67.4%	
Myomectomy	10	7.4%	5	11.6%	
Adnexal surgery	45	33.3%	9	20.9%	
Complications					1.000
Yes	132	97.8%	0	0%	
No	3	2.2%	43	100%	
Bladder injury	1	0.7%	0	0%	1.000
Bowel injury	2	1.5%	0	0%	1.000

P values for mean data were calculated with the use of independent t-test or Mann-Whitney U test, for percentages with the use of chi-square test or Fisher's exact test.
SD: standard deviation, BMI: body mass index

Discussion

Our study demonstrated that the prevalence of high patient satisfaction with the informed consent process was 75.8%. Similar findings were observed in other studies: Guzman et al[25] reported 70.7% in the Philippines, Akkad et al[27] found 80% in England, and Sulaiman et al[24] reported 77% in Saudi Arabia. The mean total score for DSS in our study was 27 (27.87 ± 2.77). This was consistent with previous studies, such as Hallock et al[21], where the mean DSS score was 27.9, and Guzman et al[25], where it was 27.4.

The consistency of our findings with other studies suggests that patient satisfaction levels are comparable across different regions and healthcare systems. The quality of a well-structured informed consent process appears to be more crucial than the specific healthcare system or region. Moreover, Akkad et al[27] (2006) found significantly higher satisfaction in non-emergency gynecological surgeries (80%) compared to emergency cases (63%). While our study focused solely on elective surgeries, the high satisfaction rate reflects patterns that observed in non-emergency settings, stress that the time to receive information and the type of procedure are affecting patient satisfaction.

Key factors that significantly impacted patient satisfaction, which can be improved through counseling, include being informed about the consequences of not undergoing the procedure, having a clear understanding of the procedure sufficient to explain it to others, understanding the reasons for prolonged urinary catheterization if necessary, and being given the opportunity to refuse

the procedure.

Regarding the results, no significant correlation was found between patient satisfaction and demographic factors such as educational background and occupation, as the distribution between the two groups was similar and all patients may receive similar standardized information and care during preoperative process leading to similar levels of understanding and satisfaction. This similarity enhanced the reliability of the findings in this context.

Although statistically significant difference between the highly satisfied and not highly satisfied groups regarding being informed about the reason for prolonged urinary catheterization if needed. However, both groups received or were aware of this information at relatively low rates, 74.1% and 58% respectively. Therefore, this issue should be emphasized to increase patient satisfaction and understanding.

As health professionals, we do understand that learning about the experience of our patients is very critical in order to enable us to offer them better quality of care. The study represented a novelty effort in the local context and has been conducted with the objective of eliciting how patients feel about their involvement in decision-making regarding their health. We based our measurements on valid tools in order to act like a sturdy bridge, thus connecting our research methods to the real-world level of patient experiences. This allows us to gather feedback directly from patients and subsequently delineate their needs and perspectives.

This study was conducted at a single institution, which limits the ability to apply the findings to other settings. The patient experiences and satisfaction levels observed here may differ from those in other institutions due to variations in practices, resources, and patient demographics. As a result, the findings may not be fully applicable to patients in other departments or hospitals. Differences in healthcare delivery, patient populations, and institutional policies across various settings could lead to different outcomes, making it challenging to generalize the results beyond this institution. Furthermore, cultural factors in Thailand, such as respect for authority and conflict avoidance, heavily influence patient interactions in medical settings. Thai patients often hesitate to voice concerns or dissatisfaction, leading to potentially inflated satisfaction ratings. Reluctance to give negative feedback is common, and patients may provide positive responses even if they have reservations. Additionally, norms discouraging questioning authority may limit patients' willingness to ask questions or seek clarification, impacting the depth of informed consent.

These and similar studies showed high satisfaction rates, which indicated a need for comprehensive approaches to the informed-consent process. Educating patients promotes satisfaction, decreases preoperative anxiety and creates trust in providers. Although our study was conducted at a single institution, limiting generalizability, the consistent findings suggest that comprehensive information provision, patient participation, and clear communication are key elements of a successful informed consent process applicable across various settings.

Conclusion

The study underscored the vital importance of a well-executed informed consent process for elective gynecological surgery in terms of patient satisfaction when communication and participation were emphasized. Future research should be conducted in other contexts and different types of population to confirm these findings, which would help us determine the adequate intervention in informed-consent process across various healthcare backgrounds.

Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Rate of Re-dating after Determination of Gestational Age using Ultrasonography in Clinically Reliable and Clinically Non-reliable Pregnant Women during the First Trimester

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ABSTRACT

Objectives: The primary outcome was to compare the rate of gestational age (GA) re-dating after determination of GA using ultrasonography (US) in clinically reliable (non-indicated US) and clinically non-reliable (indicated US) pregnant women during the first trimester. The secondary objective was to present the incidence of accidentally diagnosed abnormal pregnancy and identify the clinical factors influencing the need for GA re-dating.

Materials and Methods: This is an analytic cross-sectional study comparing the rate of GA re-dating after determination of GA using US in clinically reliable and clinically non-reliable pregnant women, as well as presenting the incidence of GA re-dating among pregnant women overall and incidence of accidentally diagnosed abnormal pregnancy, comparing the discrepancy in duration of pregnancy between clinically reliable and clinically non-reliable groups.

Results: A total of 119 participants were enrolled. After US, 11 (11/119, 9.24%) participants received an abnormal or complicated pregnancy diagnosis. The rate of participants who needed GA re-dating and had an abnormal pregnancy diagnosis in the clinically non-reliable and clinically reliable groups were similar. 23 in 51 (45.1%) participants in clinically non-reliable were needed GA re-dating and 25 in 57 (52.1%) participants in clinically reliable were needed GA re-dating, ($p = 0.995$). If GA re-dating was needed, there was no statistically significant difference in the median number of days of GA re-dating between the clinically non-reliable and clinically reliable groups [10 (interquartile range (IQR) 07.00-21.00) vs 12 (IQR 8.00-15.00) days, $p = 0.872$).

Conclusion: Nearly half of the pregnant women needed GA re-dating when undergoing US in the first trimester of pregnancy. The rate of GA re-dating was similar in the clinically reliable and clinically non-reliable groups without any hint of clinical factor influence. Approximately 10% of participants found an abnormal pregnancy diagnosis. Eight percent found abnormal pregnancy in clinically reliable groups.

Keywords: gestational age, corrected, ultrasonographic, indicated, non-indicated

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สัดส่วนการปรับอายุครรภ์ใหม่หลังการประเมินอายุครรภ์โดยการตรวจคลื่นเสียงความถี่สูงในหญิงตั้งครรภ์ที่ข้อมูลทางคลินิกเชื่อถือได้ กับไม่ได้ช่วงไตรมาสแรกของการตั้งครรภ์

สุพพดา ฉัตรตระกูลพงษ์, กิตติพงษ์ คงสมบูรณ์, ธารางรัตน์ หาญประเสริฐพงษ์

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อเปรียบเทียบสัดส่วนของหญิงตั้งครรภ์ไตรมาสแรกที่ปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูงระหว่างหญิงตั้งครรภ์ที่ข้อมูลทางคลินิกเชื่อถือได้ (ไม่มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ (มีข้อบ่งชี้) วัตถุประสงค์รองเพื่อแสดงอุบัติการณ์การตั้งครรภ์ผิดปกติโดยบังเอิญ และแสดงปัจจัยทางคลินิกที่มีผลต่อการปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูง*

วัสดุและวิธีการ: *การศึกษาแบบวิเคราะห์ตัดขวางเปรียบเทียบสัดส่วนของหญิงตั้งครรภ์ไตรมาสแรกที่ปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูงระหว่างหญิงตั้งครรภ์ที่ข้อมูลทางคลินิกเชื่อถือได้ (ไม่มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ (มีข้อบ่งชี้) แสดงอุบัติการณ์การปรับอายุครรภ์ใหม่และการพบการตั้งครรภ์ผิดปกติโดยบังเอิญของหญิงตั้งครรภ์ทั้งหมด และเปรียบเทียบความคลาดเคลื่อนในระยะเวลาตั้งครรภ์ระหว่างกลุ่มที่ข้อมูลทางคลินิกเชื่อถือได้กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ และยังระบุปัจจัยทางคลินิกที่มีอิทธิพลต่อความจำเป็นในการปรับอายุครรภ์*

ผลการศึกษา: *มีหญิงตั้งครรภ์เข้าร่วมการศึกษา 119 คน หลังตรวจคลื่นเสียงความถี่สูงหญิงตั้งครรภ์ 11 ใน 119 (ร้อยละ 9.24) ตรวจพบการตั้งครรภ์ผิดปกติ สัดส่วนของหญิงตั้งครรภ์ไตรมาสแรกที่ปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูงและอุบัติการณ์การพบการตั้งครรภ์ผิดปกติระหว่างหญิงตั้งครรภ์ที่ข้อมูลทางคลินิกเชื่อถือได้ (ไม่มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ (มีข้อบ่งชี้) ไม่มีความแตกต่างกัน 23 ใน 51 (ร้อยละ 45.1) และ 25 ใน 57 (ร้อยละ 52.1) หญิงตั้งครรภ์ ที่ข้อมูลทางคลินิกเชื่อถือไม่ได้ (มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือได้ในการประเมินอายุครรภ์ (ไม่มีข้อบ่งชี้) มีการปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูง ($p = 0.995$). พิจารณาเฉพาะกลุ่มที่ต้องปรับอายุครรภ์ใหม่ ค่ากลางจำนวนวันที่ต้องมีการปรับระหว่างหญิงตั้งครรภ์ที่ข้อมูลทาง*

คลินิกเชื่อถือได้ (ไม่มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ (มีข้อบ่งชี้) ไม่มีความแตกต่างกัน

***สรุป**: สัดส่วนของหญิงตั้งครรภ์ไตรมาสแรกที่ปรับอายุครรภ์ใหม่หลังตรวจประเมินอายุครรภ์ด้วยคลื่นเสียงความถี่สูงระหว่างหญิงตั้งครรภ์ที่ข้อมูลทางคลินิกเชื่อถือได้ (ไม่มีข้อบ่งชี้) กับอาการทางคลินิกเชื่อถือไม่ได้ในการประเมินอายุครรภ์ (มีข้อบ่งชี้) ไม่มีความแตกต่างกัน เกือบครึ่งของหญิงตั้งครรภ์จำเป็นต้องปรับอายุครรภ์ใหม่เมื่อตรวจคลื่นเสียงความถี่สูงช่วงไตรมาสที่ 1 โดยไม่มีข้อมูลทางคลินิกใดชี้นำ ประมาณร้อยละ 10 ของหญิงตั้งครรภ์ในการศึกษานี้ตรวจพบการตั้งครรภ์ผิดปกติจากการตรวจด้วยคลื่นเสียงความถี่สูง*

***คำสำคัญ**: อายุครรภ์, แก้ไขแล้ว, คลื่นเสียงความถี่สูง, มีข้อบ่งชี้, ไม่มีข้อบ่งชี้*

Introduction

Accurate gestational age (GA) is an important part of fetal growth assessment, abnormal maternal and fetal diagnosis and planning of pregnancy management. Clinical information such as the last menstrual period (LMP), uterine size, and maternal perception of quickening accompanied by obstetric ultrasonography (US) are usually provided for GA documentation. Obstetric US measurement of mean gestational sac diameter (MSD), fetal crown-rump length (CRL) and biometric measurement, including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL), are commonly used for US determination of GA[1]. The parameters chosen depend on fetal size and GA[1]. In Thailand, however, the Royal Thai College of Obstetricians and Gynecologists has used a prenatal guideline which states it would prefer Thai obstetricians to confirm fetal GA using ultrasonography since the year 2023[2]. Furthermore, regarding the availability of routine ultrasonography in general practice in Thailand, the situations of developing limited resources still differ between places. In private clinics or hospitals, nearly all pregnant women have their determined GA confirmed by US during the first antenatal care visit. This contrasts with rural areas, where determination of GA using clinical data is generally practiced. A study conducted by Sritippayawan et al found that among Thai women, GA re-dating after ultrasound occurred in about 25.4% of pregnancies[1]. Research on the use of US for GA determination is limited to clinically non-reliable (indicated US) cases. However, the incidence of GA re-dating after US examination for GA determination in pregnant women in Thailand is present in both clinically reliable (non-indicated US) and clinically non-reliable (indicated US) groups. Thus, we conducted this study. The main purpose of this study was to compare the incidence of GA re-dating after US examination for GA determination in pregnant women in Thailand between clinically reliable and clinically non-reliable groups. The second purpose was to present the incidence of GA re-dating in pregnant women overall, and the incidence of accidentally diagnosed abnormal pregnancy, such as multifetal gestations, embryonic/fetal demise, gestational trophoblastic disease, etc., as well as compare the discrepancy in duration of pregnancy between clinically reliable and clinically non-reliable groups. Finally, we identified clinical factors influencing the need for GA re-dating.

Materials and Methods

This analytic, cross-sectional study was conducted with healthy pregnant women who were scheduled for antenatal visits at the Antenatal Outpatient Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot

University, Thailand, between December 2022 and September 2023 and had a GA diagnosis bases on the clinical history less than 14 weeks. The exclusion criterion was as follows: pregnant women who had previously been documented for GA using US. The study was approved by the institute's ethics committee (SWUEC/E/M-068/2565) and was registered on the Thai Clinical Trials Registry (TCTR 20221022001). Informed consent from all participants was obtained.

The participants were asked to give their personal information, which included their maternal age, education level, parity, gravidity, occupation, religion, family income and LMP. Then, the clinical information for evaluating the reliability of clinically determined GA was asked for, which included regularity of menstruation, how they remembered the LMP, duration of hormonal contraceptive discontinuation, abnormal vaginal bleeding after pregnancy diagnosis, history of inpatient care for hyperemesis gravidarum, risk of multiple gestations and history of severe pelvic adhesion. Then, physical examination for uterine size was performed. Pelvic examination was not routinely performed. The date-size discrepancy was only diagnosed by abdominal examination. The participants were categorized into two groups: a clinically reliable (non-indicated US) group and a clinically non-reliable group (indicated US). A participant was defined as clinically non-reliable (indicated US) if she could not remember her last menstrual period, had an irregular menstrual cycle, had a menstrual interval of less than 21 or more than 35 days, had conceived during oral hormonal contraception use or within 24 weeks after receiving the last injectable hormonal contraception, had a history of multiple gestations in her family, had a history of abnormal vaginal bleeding in the current pregnancy, had significant pelvic pain, had a presence of hyperemesis gravidarum, or had a presence of date-size discrepancy[4]. Then, all participants underwent obstetric US examination performed by the last author listed in this study (T.H.), who became qualified in maternal fetal medicine practice at the Royal Thai College of Obstetricians and Gynaecologists (RTCOG) and had more than 15 years of experience in obstetric US. Abdominal (Abd) US was firstly performed in all participants and vaginal US was performed if the Abd US did not successfully depict an image which was proper enough for pregnancy identification and GA determination. Our US steps were as follows: A survey of the pelvic organ and evaluation of the presence or absence of an intrauterine gestational sac (IUGS) was performed. Then, if an IUGS was present, the presence of a yolk sac (YS) or embryo/fetus was subsequently documented. When an embryo/fetus was present, GA was determined based on CRL measurement (mean of three discrete measurements). If an IUGS was present without an embryo/fetus, undetermined pregnancy was recorded, and a follow-up appointment was made with the participant. In the present study, GA was determined by a fetus/embryo measurement. When the CRL was beyond 84 mm in length (approximately 140 weeks of gestation), a combination of BPD, HC, AC and FL measurement was used for GA determination. The recommended guideline for re-dating based on US is classified according to a GA range based on LMP[5]:

a. $\leq 8^{6/7}$ weeks of gestation: re-date when there is a discrepancy of more than 5 days between US dating and LMP or clinical dating.

b. $9^{0/7}$ to $13^{6/7}$ weeks of gestation: re-date when there is a discrepancy of more than 7 days between US dating and LMP or clinical dating.

c. $14^{0/7}$ to $15^{6/7}$ weeks of gestation: re-date when there is a discrepancy of more than 7 days between US dating and LMP or clinical dating.

d. $16^{0/7}$ to $21^{6/7}$ weeks of gestation: re-date when there is a discrepancy of more than 10 days between US dating and LMP or clinical dating.

Abnormal pregnancies, such as multiple gestations, anembryonic gestation, ectopic pregnancy, and embryonic/fetal demise, were recorded. The results of the US examination were recorded in a hospital-based system and reported to the primary doctor for antenatal management planning.

The required sample size was estimated by

using a formula for two independent proportions. In a previous study, 85% of pregnant women who were clinically non-reliable needed their GA re-dated after US. We expected that about 55% of the pregnant women who were clinically reliable would need their GA re-dated after US. To achieve an alpha error of 0.05 and a beta error of 0.1, the sample sizes required were around 47 participants for each group. Allowing for 15% lost or missing data, an approximate total of 110 participants were required.

The baseline characteristics of the participants within each group were examined by tabulating percentages, means and standard deviation. The numbers of participants who needed GA re-dating and had an abnormal pregnancy diagnosis were compared between the clinically non-reliable and the clinically reliable groups using the chi-square test. The difference in number of days in the participants needing GA re-dating between the clinically non-reliable and the clinically reliable groups was presented as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Lastly, the possible factors associated with all participants who needed GA re-dating were identified using the independent t-test, chi-square test or Fisher's exact test. In all statistical tests, p values of < 0.05 were considered significant.

Results

A total of 119 pregnant women were enrolled in the study and divided into two groups of 57 and 62 participants in the clinically non-reliable and the clinically reliable group, respectively. After US, 11 (11/119, 9.24%) participants received an abnormal or complicated pregnancy diagnosis. The details of abnormal pregnancy are presented in Fig. 1. There were six (6/57, 10.53%) and five (5/62, 8.06%) participants in the clinically non-reliable and the clinically reliable groups, respectively, who were excluded from analysis because of abnormal pregnancy. Thus, 51 and 57 participants in the clinically non-reliable and the clinically reliable groups, respectively, were eventually analyzed (Fig. 1).

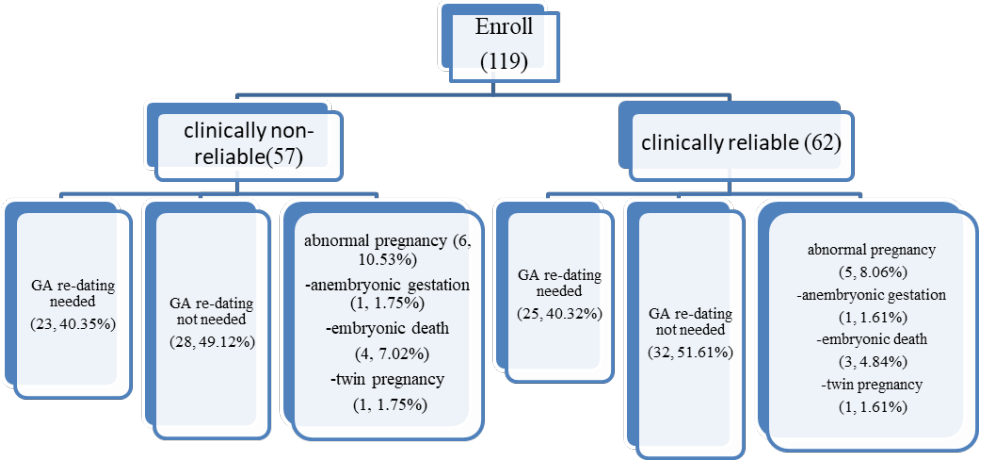

Fig. 1. Study diagram.

GA: gestational age

Table 1 presents the participants' baseline characteristics in both groups. The data in the two groups were compared. Table 2 presents a comparison of the numbers of participants who needed GA re-dating and had an abnormal pregnancy diagnosis between the clinically non-

reliable and the clinically reliable groups. They were similar in both groups. Table 3 presents a comparison of the difference in number of days in the participants needing GA re-dating between the clinically non-reliable and the clinically reliable groups. When focusing on participants needing GA re-dating, the difference in the number of days of GA re-dating between the clinically non-reliable and the clinically reliable groups was not statistically significant [10 (IQR 7.00-21.00) vs 12 (IQR 8.00-15.00) days, p = 0.872). Table 4 presents the possible factors associated with the need for GA re-dating. None of any clinical factors, which were useful to guidance it.

Table 1. Baseline characteristics (n = 119).

Characteristic	clinically reliable (n = 57)	clinically non-reliable (n = 62)
Age (years), mean ± SD	28.57 ± 6.031	28.86 ± 4.764
Religion, n (%)		
- Buddhist	47 (82.4)	51 (82.3)
- Muslim	9 (15.8)	8 (12.9)
- Christ	1 (1.8)	3 (4.8)
Occupation, n (%)		
- Employee	17 (29.8)	21 (33.9)
- Housewife	4 (7.0)	4 (6.5)
- Government officer	12 (21.1)	16 (25.8)
- Others	24 (42.1)	21 (33.9)
Location, n (%)		
- Nakhon Nayok	29 (50.9)	26 (41.9)
- Pathum Thani	22 (38.6)	33 (53.2)
- Bangkok	3 (5.3)	0 (0.0)
- Others	3 (5.3)	3 (4.8)
Level of education, n (%)		
- Less than primary school	21 (36.8)	14 (22.6)
- Primary school-bachelor	35 (61.4)	47 (75.8)
- Higher than bachelor	1 (1.8)	1 (1.6)
Family income (Bath)		
- < 15,000	15 (26.3)	12 (19.4)
- 15,000 – 29,999	26 (45.6)	23 (37.1)
- 30,000 – 50,000	15 (26.3)	22 (35.5)
- > 50,000	1 (1.8)	5 (8.1)
Primigravida, n (%)		
- Yes (G = 1)	22 (38.6)	33 (53.2)
- No (G ≥ 2)	35 (61.4)	29 (46.8)
Nulltiparous, n (%)		
- yes (p = 0)	26 (45.6)	34 (54.8)
- no (p ≥ 1)	31 (54.4)	28 (45.2)
History of abortion, n (%)		
- Yes	18 (31.6)	13 (21.0)
- No	39 (68.4)	49 (79.0)
GA based on LMP, n (%)		
- GA ≤ 8^{+6} weeks	29 (50.9)	29 (46.8)
- GA > 9 weeks	28 (49.1)	33 (53.2)

SD: standard deviation, GA: gestational age, LMP: last menstrual period

Table 2. Comparisons of the number of participants who gestational age re-dating needed and abnormal pregnancy diagnosis between clinically reliable and clinically non-reliable groups.

Group		Clinically non-reliable (51)	Clinically reliable (57)	Relative risk	95% CI	p value*
GA re-dating needed, n (%)	Yes (%)	23 (45.1)	25 (43.9)	1.001	0.674-1.488	0.995
	No (%)	28 (54.9)	32 (56.1)	-	-	-
Abnormal pregnancy diagnosis, n (%)	Yes (%)	6 (11.8)	5 (8.8)	1.133	0.638-2.011	0.686
	No (%)	45 (88.2)	52 (91.2)	-	-	-

* Chi-square test
CI: confidence interval

Table 3. Comparisons of the number of day difference in gestational age re-dating needed par-ticipants between clinically reliable and clinically non-reliable groups.

Group	Day		p value*
	Median	IQR	
clinically non-reliable	10	07.00 - 21.00	0.872
clinically reliable	12	08.00 - 15.00	

* Mann-Whitney U test
IQR: interquartile range

Table 4. Possible factors associated with gestational age re-dating needed.

Factors	GA re-dating needed (n = 48)	GA re-dating not needed (n = 60)	Relative risk	95% CI	p value
Religion, n (%)					
- Buddhist	40 (83.3)	54 (90.0)	0.898	0.529 - 1.525	0.699*
- Muslim and Christ	8 (16.7)	6 (10.0)			
Occupation, n (%)					
- Employee	18 (37.5)	18 (30.0)	1.242	0.812 - 1.900	0.330*
- Others	30 (62.5)	42 (70.0)			
Location, n (%)					
- Nakhon Nayok	46 (95.8)	59 (98.3)	1.168	0.465 - 2.933	1.000**
- Others	2 (4.2)	1 (1.7)			
Level of education, n (%)					
- Less than primary school	18 (37.5)	16 (26.7)	1.349	0.887 - 2.052	0.178*
- Primary school - higher than bachelor	30 (62.5)	44 (73.3)			
Family income (Bath)					
- < 15,000	10 (20.8)	15 (25.0)	0.903	0.529 - 1.540	0.701*
- ≥ 15,000	38 (79.2)	45 (75.0)			
Primigravida, n (%)					
- Yes (G = 1)	20 (41.7)	31 (51.7)	0.838	0.544 - 1.292	0.420*
- No (G > 1)	28 (58.3)	29 (48.3)			

* Chi-square test, **Fisher's exact test
GA: gestational age, CI: confidence interval

Discussion

GA is an important piece of information for obstetric care planning and management. Although the prenatal guideline which was announced by the RTCOG suggested dating GA using US for all pregnant women as early as possible, it is still not available due to the reasons of limited resources and performance of clinical practice according to the familiarity of public health personnel. In any case, most Thai practice guidelines on obstetric care management reference studies from developed countries. The current study is the first study which has evaluated the rate of GA re-dating after US examination during first-trimester prenatal care, dividing the patients into clinically reliable and clinically non-reliable groups using the decisions made by physicians after analyzing patient histories and performing physical examinations. The rationale behind this study is the actual practice in Thailand. Therefore, our findings represent the real situation in our country and may be useful for other developing countries. In the current study, we found that the classification of the pregnant women into clinically reliable or non-reliable groups was sometimes difficult and awkward due to patient recall of the LMP date, and morning sickness symptoms without serum electrolyte assessment that should have been assessed for hyperemesis gravidarum. Our study found that 57/119 (47.89%) of participants were indicated for US, mainly due to the fact they could not recall their menstrual period. This incidence was comparable to that of a previous study, which found that approximately one half of pregnant women could accurately recall their LMP[5-7]. In our study, we classified participants as reasonably as possible. According to the results presented, nearly half (59/119, 49.58%) of all participants needed GA re-dating or were found to have an abnormal pregnancy which needed specific obstetric management. The rate of participants needing GA re-dating was quite high. Moreover, the rates of participants needing GA re-dating were compared between the clinically non-reliable and the clinically reliable groups (47.9% vs 52.1%, prevalence rate ratio = 1.001, p = 0.995). This indicates that clinical information might not be properly used for GA determination. If there is no US performance, nearly half of all pregnant women may have a non-reliable GA until further gestation. The reasons for clinical non-reliability in this study and previous studies, such as inability to remember the exact date of menstruation because of amenorrhea, irregular menstrual cycles, abnormal vaginal bleeding during the current pregnancy and use of hormonal contraception, were similar[6]. Previous studies, most of which were carried out more than 10 years ago, had a GA of enrolled participants which was higher than that of our current study and used the second trimester US fetal biometry (BPD) for the studies[6-9]. However, critical concerns regarding universal US were postulated by previous studies, which were financial factors, operator exhaustion, and female feticide, in some settings[9-10]. In Thailand, financial factors and operator exhaustion were also concerns, and this may be similar in settings of other developing countries where US is still a limited resource. Female feticide may be less concerning in our study because US was performed before 14 weeks of gestation, which is a period when sex determination is not definitely accurate, especially before 12 weeks of gestation[11]. A previous study reported an accuracy of approximately 91% in the 11th and 12th week of pregnancy[12]. Moreover, non-invasive prenatal testing has been found to be more accurate than US for sex determination at similar earlier GA to those in our study[13]. In order to provide suggested GA for use with US aiming for GA determination, previous studies included participant GA which were higher than those in our current study. Interestingly, the incidence of GA needing re-dating was similar[14-15]. Thus, we suggest that GA determination be performed as early as possible. A GA of less than 14 weeks is preferred because the larger fetal measurement introduces greater variability of GA determination. In any case, CRL measurement is more suggested than mean sac diameter measurement[5]. In the reliable group, the need for re-dating may arise from variations in the

interval periods. Errors are more likely when evaluation is delayed. Moreover, another benefit of US during the first trimester is the accidental detection of abnormal or complicated pregnancies such as embryonic/fetal death, anembryonic gestation and multiple pregnancies[16]. Determination of twin chorionicity has been found to be more accurate in early pregnancy than in later pregnancy[17]. In other 2 studies published in BMC Pregnancy and Childbirth, both studies underscored the significance of early ultrasound in Asian populations, including Thailand, for accurately determining GA and reducing the incidence of re-dating. They highlighted the utility of early ultrasound as a critical tool in prenatal care, ensuring better pregnancy management outcomes[18-19].

Our study is the first study which has evaluated the number of days difference in participants needing GA re-dating between the clinically non-reliable and the clinically reliable groups. The median values of the number of days difference were around 10 and 12 days in the clinically non-reliable and the clinically reliable groups, respectively, and were comparable. We feel that more than 10 days difference is clinically important for obstetric decision-making in the case of pregnancy complications such as preterm labor, premature rupture of membranes or occurrence of abnormal bleeding. In the incidence of needing GA re-dating, both abnormal pregnancy detection and the number of days difference support an obstetrician's decision to perform US during the first trimester of pregnancy with all pregnant women regardless of whether clinical information is necessary or not.

Besides that, we were interested in finding out the possible factors associated with the need for GA re-dating. Our study failed to identify any significant possible factors associated with needing GA re-dating, including religion, occupation, living location, level of education, economic status and gravidity. This was different from a previous study which found that there was a trend toward expected-due-date modification with increasing gravidity[14]. This may have been caused by the difference in main outcome measurement. We focused on GA re-dating which was classified by the range of duration, but the previous study focused on the point of expected-due-date modification. In any case, the influence of this factor was found only to be a trend but was not strongly associated. Therefore, we support universal US examination for GA determination as early as possible without clinical factor adjustment.

The association of early GA re-dating using US with pregnancy and neonatal outcome has not been covered in the present study. This was a limitation of our study. A previous study showed that pregnancy dating using the LMP alone tended to overestimate the duration of gestation[9]. This study was a retrospective study and the GA of most of their participants was more than 10 weeks of gestation (22% of participants had a GA of less than 10 weeks). Thus, the pregnancy and neonatal outcome may be differently found. Therefore, further study is planned.

Conclusion

In conclusion, nearly half of the pregnant women needed GA re-dating when undergoing US in the first trimester of pregnancy. The rate of GA re-dating was similar in the clinically reliable and clinically non-reliable groups without any hint of clinical factor influence. Therefore, we suggest universal US aiming for GA determination as much as and as early as possible.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

The Effects of Vitamin C for Iron Supplementation during Pregnancy with Risk of Anemia: A randomized controlled clinical trial

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ABSTRACT

Objectives: To evaluate the effects of combining vitamin C with iron supplementation on hemoglobin (Hb) and hematocrit (Hct) levels among pregnant women at high risk of anemia.

Materials and Methods: A randomized controlled trial was conducted among singleton pregnant women at 14-28 weeks of gestation, with Hb ≥ 10.5 g/dL, Hct ≥ 32% and ferritin ≥ 30 ng/mL, who were at risk of anemia (> prior 2 pregnancies, age < 18 or > 35 year-old or body mass index < 18 kg/m^2). Women attending Rajavithi Hospital from July 2023 - June 2024 were randomly assigned to receive vitamin C (500 mg) plus iron supplement or iron only. Hb and Hct were measured 2 months after intervention.

Results: Total of 100 enrolled participants, 22 (22%) were excluded for having ferritin levels < 30 ng/mL. The remaining 78 women were randomized, with 38 in the experimental group (vitamin C plus iron) and 40 in the control group (iron only). There were no significant differences in Hb and Hct levels between the two groups, both initially and 2 months after the intervention (Hb: mean difference (MD) -0.11; 95% CI -0.53, 0.31; p = 0.609 and MD -0.24; 95% CI -0.67, 0.32; p = 0.253; respectively) (Hct: MD -0.77; 95% CI -1.96, 0.55; p = 0.266; MD -0.70; 95% CI -1.97, 0.58; p = 0.282). The repeated measure analysis of variance (ANOVA) showed non-significant overall mean differences. No adverse events were reported.

Conclusion: Vitamin C was not essential with iron supplements to improve Hb and Hct levels in pregnant women at risk of anemia.

Keywords: vitamin C, hemoglobin, hematocrit, risk of anemia in pregnancy, iron supplement.

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ประสิทธิภาพของการให้วิตามินซีร่วมกับธาตุเหล็กในหญิงตั้งครรภ์ที่มีความเสี่ยงต่อภาวะโลหิตจาง : การศึกษาทดลองแบบสุ่ม

ลลิตพันธุ์ ศรีมณีศิริ, ลัลธพร พัฒนาวิจารย์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบระดับฮีโมโกลบิน (Hemoglobin) และฮีมาโตคริต (Hematocrit) ระหว่างกลุ่มที่ได้รับประทานวิตามินซีร่วมกับธาตุเหล็ก กับกลุ่มที่รับประทานธาตุเหล็กเพียงอย่างเดียว*

วัสดุและวิธีการ: *การแบ่งกลุ่มแบบสุ่มในหญิงตั้งครรภ์เดี่ยวอายุครรภ์ 14-28 สัปดาห์ ที่มีระดับฮีโมโกลบินมากกว่าหรือเท่ากับ 10.5 กรัมต่อเดซิลิตร ฮีมาโตคริตมากกว่า 32 เปอร์เซ็นต์ และระดับเฟอริตินมากกว่าหรือเท่ากับ 30 นาโนกรัมต่อมิลลิลิตร ที่มีความเสี่ยงต่อภาวะซีด (ได้แก่ เคยตั้งครรภ์มากกว่า 2 ครั้ง, อายุน้อยกว่า 18 ปี หรือมากกว่า 35 ปี, ดัชนีมวลกายน้อยกว่า 18 กิโลกรัม ต่อตารางเมตร) ระหว่างเดือนกรกฎาคม 2566 ถึงเดือนมิถุนายน 2567 โดยแบ่งสุ่มเป็นกลุ่มที่ได้รับการเสริมวิตามินซี 500 มิลลิกรัมร่วมกับเหล็ก หรือ การเสริมเหล็กเพียงอย่างเดียว และติดตามการเพิ่มของระดับฮีโมโกลบินและฮีมาโตคริตใน 8 สัปดาห์*

ผลการศึกษา: *จากผู้เข้าร่วมการวิจัยทั้งหมด 100 คน 22 คนถูกคัดออกเนื่องจากระดับเฟอริตินต่ำกว่า 30 คงเหลือ 38 คนในกลุ่มทดลอง (วิตามินซีร่วมกับเหล็ก) 40 คนในกลุ่มควบคุม (เหล็กอย่างเดียว) มี 1รายในกลุ่มนี้ออกจากการศึกษาเนื่องจากทารกเสียชีวิตในครรภ์ ผลพบว่าที่ 8 สัปดาห์ถัดมา ไม่มีความแตกต่างในระดับฮีโมโกลบินและฮีมาโตคริตระหว่าง 2 กลุ่ม (ฮีโมโกลบิน ค่าเฉลี่ยความแตกต่างอยู่ที่ -0.11; 95%CI -0.53, 0.31; p = 0.609 ในกลุ่มทดลองและ -0.24; 95%CI -0.67, 0.32; p = 0.253 ในกลุ่มควบคุม ส่วนฮีมาโตคริตมีค่าเฉลี่ยความแตกต่างอยู่ที่ -0.77; 95%CI -1.96, 0.55; p = 0.266 ในกลุ่มทดลองและ -0.70; 95%CI -1.97, 0.58; p = 0.282 ในกลุ่มควบคุม ไม่มีรายงานภาวะไม่พึงประสงค์จากการรับประทานยา*

สรุป: *การเสริมวิตามินซีร่วมกับเหล็กไม่มีความสำคัญในการเพิ่มระดับฮีโมโกลบินและฮีมาโตคริตในหญิงตั้งครรภ์ที่มีความเสี่ยงต่อภาวะโลหิตจาง*

คำสำคัญ: *วิตามินซี, ฮีโมโกลบิน, ฮีมาโตคริต, สตรีตั้งครรภ์ที่มีความเสี่ยงต่อภาวะซีด, การเสริมเหล็ก*

Introduction

During pregnancy, the blood volume increases by an average of 50% above the non-pregnant level by 34 weeks of gestation[1]. This increase meets the metabolic demands of the enlarged uterus and ensures a sufficient supply of nutrients and elements to support the rapidly growing placenta and fetus. During blood volume expansion, the plasma volume and the erythrocyte mass increase. The average increase in the erythrocyte volume is around 450 mL. However, because the increase in the plasma volume is greater than the increase in the erythrocyte mass, the hemoglobin (Hb) and hematocrit (Hct) levels tend to decrease slightly[2]. On average, the Hb level reaches about 12.5 g/dL, with approximately 5% of pregnant women presenting an Hb level below 11.0 g/dL, particularly in late pregnancy and often due to iron deficiency. Hb is crucial for transporting oxygen in the blood and protecting mothers from complications during childbirth[1,2].

Anemia is a condition characterized by an insufficient number of red blood cells to meet the body's physiological needs. According to the World Health Organization (WHO) guidelines[3], an Hb level below 11.0 g/dL is indicative of anemia in pregnant women. However, according to the American College of Obstetricians and Gynecologists (ACOG) practice bulletin[3], anemia in pregnancy is defined by Hb and Hct levels below 11 g/dL and 33%, respectively, in the first trimester; 10.5 g/dL and 32%, respectively, in the second trimester; and 11 g/dL and 33%, respectively, in the third trimester. Iron deficiency is considered to be the most common cause of anemia. Ferritin has the highest sensitivity and specificity for diagnosing iron-deficiency anemia, with a level below 30 µg/L confirming this condition[4].

In 2019, the global prevalence of anemia among women of reproductive age was 29.9% (95% uncertainly interval [UI] 27.0%, 32.8%), while the prevalence among pregnant women was 36.5% (95% UI 34.0%, 39.1%)[5]. The prevalence of anemia in Thai population in first antenatal care as 6.92%, third trimester was 24.62% and intrapartum period was 4.76%[6]. The prevalence of iron deficiency in early pregnancy Thai population was reported to be 15.2%[7]. The factors associated with anemia include age, gender, residential area, and smoking habits. Additionally, studies have identified correlations with multiple pregnancies (> 2)[5,8,9], teenage pregnancy[8,9], maternal age over 35 years[5], and a low pre-pregnancy body mass index (BMI)[8]. Among pregnant women, iron deficiency anemia is also linked to adverse pregnancy outcomes such as an increased risk of gestational diabetes (15.9%), fetal oxygen abnormalities leading to fetal non-reassuring status (9.4%), preterm delivery (8.2%), a low amniotic fluid level (1.95%), neonatal complications (10.6%), critical care admissions (9.7%), and a low birth weight (4.9%). Moreover, anemia significantly raises the likelihood of requiring blood transfusions during pregnancy[5,8].

The WHO recommends daily oral supplementation of iron and folic acid, with 30-60 mg/day of elemental iron, for pregnant women to prevent maternal anemia[11]. Iron supplements can be administered orally, intramuscularly, or intravenously; each method offers its own benefits and potential side effects. Oral supplementation is generally preferred due to its efficiency, affordability, and safety. Vitamin C enhances iron absorption by helping to reduce ferric iron through the enzyme duodenal cytochrome B (DCYTB), which transfers electrons from intracellular ascorbate. This process underscores the importance of vitamin C in improving iron absorption. Additionally, vitamin C contributes to the formation of low-molecular-weight iron chelates, further increasing iron absorption. It is also linked to erythropoiesis as well as the storage and mobilization of ferritin[12]. Numerous studies have demonstrated that combining vitamin C with iron supplementation significantly increases Hb and Hct levels, making it a safe option for pregnant women and their babies[13]. The objective of this study was to evaluate the effect of combining vitamin C with iron supplementation on Hb and Hct levels in pregnant women at high risk of anemia. Since the goal of this research is to prevent anemia during pregnancy and reduce associated

risks, the study specifically focuses on high-risk groups.

Materials and Methods

This open label randomized controlled clinical trial (CinicalTrials.gov ID. NCT05975125) was conducted between July 2023 and June 2024 at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand. The study protocol was approved by the Rajavithi Hospital ethics committee (number 118/2566, issued on June 28, 2023). All participants were informed about the study and signed a consent form. For participants under 18 years of age, informed consent was obtained from their parent or guardian.

The baseline Hb, Hct, and ferritin serum levels were measured. Then, the participants were randomly divided into two groups: the experimental group received vitamin C (500 mg) in addition to iron supplementation (triferdine, 1 tablet daily, containing iodine 150 µg, ferrous fumarate 185 mg, and folic acid 400 µg). The control group received only iron supplementation (Fig. 1). All women in this study received standard antenatal care and nutritional guidance. The iron supplement and vitamin C were started at a gestational age range between 14 and 28 weeks. All participants were prohibited from taking other medications or supplementary foods at the time of taking the medication. Two months after the trial, the Hb and Hct levels were measured again. Data on dietary habits; the possible side effects of vitamin C; and pregnancy outcomes, including postpartum hemorrhage, blood transfusion, infant weight, gestational age at delivery, and postpartum infant health, were collected. Compliance was monitored by counting the actual number of iron and vitamin C tablets that were returned. All data were analyzed to compare the outcomes between the two groups.

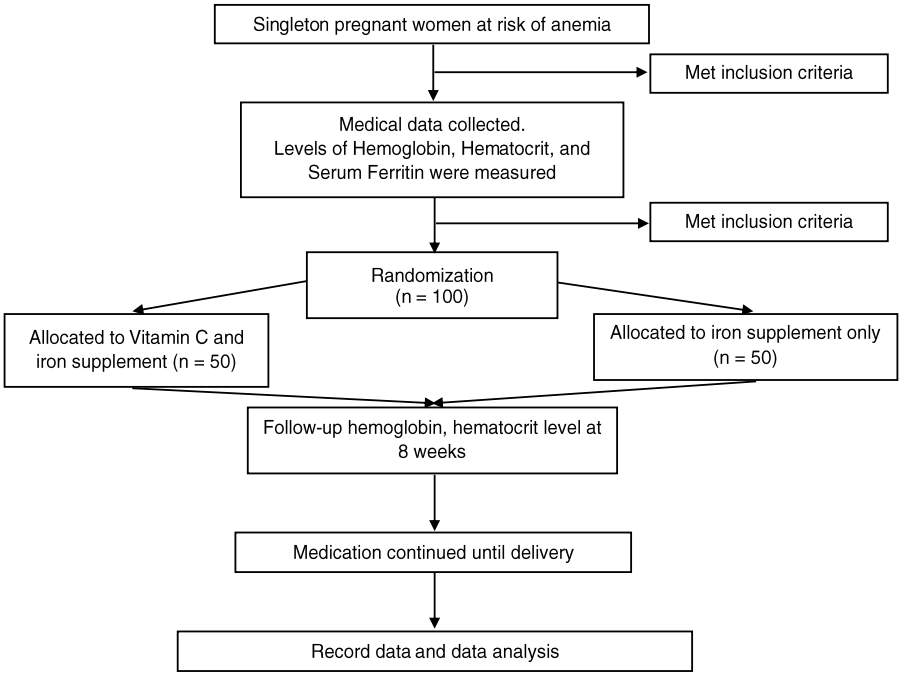

Fig. 1. Consort flow diagram

The primary objective was to compare the ability of iron supplementation, with and without vitamin C, to increase the Hb and Hct levels in pregnant women at high risk of anemia. The secondary objective was to compare pregnancy outcomes between women taking vitamin C plus iron and those

taking iron alone. Pregnant women receiving prenatal care at Rajavithi Hospital and who voluntarily participated in the research project were included. The inclusion criteria were: women with a singleton pregnancy; gestational age between 14 and 28 weeks; and at high risk of anemia due to at least one factor, such as having more than two previous pregnancies, teenage pregnancy, age over 35 years old, or a BMI under 18 kg/m^2. Additionally, the participants needed to be non-anemic, with an Hb level ≥ 10.5 g/dL and an Hct level ≥ 32% for their initial prenatal blood test. The exclusion criteria were: a ferritin level < 30 ng/mL (iron deficiency anemia, based in the ACOG recommendation); received vitamin C supplements during the study; human immunodeficiency virus (HIV) infection; iron deficiency anemia; blood disorders such as thalassemia (either carrier or severe disease), gastrointestinal bleeding, or antepartum hemorrhage; allergy to vitamin C and/or iron; chronic conditions such as kidney disease, liver disease, rheumatism, and abnormal bleeding disorders; a history of iron supplementation within the past 3 months; received blood components within the past 3 months or during the study; and gave birth within the first 2 months of participating in the study. The eligible participants were evenly assigned to the experimental group or the control group at a 1:1 ratio. The randomization process used blocks of 4, meaning that for every set of four participants, an equal number were allocated to each group.

The sample size was calculated based on a previous study[14] by using the following formula.

$$n = \frac{(Z_{\alpha/2}+Z_{\beta})^2 \times (\sigma_1^2+\sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

$$n = \frac{(1.96+0.842)^2 \times (10.89^2+11.43^2)}{(0.83 - 0.84)^2}$$

where n is the sample size, α is 0.05, $Z_{\alpha/2}$ is 1.96, Z_{β} is 0.842, $\sigma 1$ is 0.83, $\sigma 2$ is 0.84, $\mu 1$ is 10.89, and $\mu 2$ is 11.43. The calculation indicated the need for at least 38 participants per group. Considering a 30% drop-out rate, the total sample size was at least 50 participants per group.

SPSS Statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The continuous variables were presented as the mean ± standard deviation (SD) or the median. The categorical variables were presented as the number and frequency. The participant characteristics were compared the two groups using the chi-square test, Fisher's exact test, or the Mann–Whitney U test. The Hb and Hct levels were analyzed using repeated-measures analysis of variance (ANOVA). A p value of < 0.05 was considered to be statistically significant.

Results

We recruited a total of 100 women with a singleton pregnancy. We excluded 22 participants (22%) with a ferritin serum level < 30 ng/mL. We randomized the remaining 78 women: 38 into the experimental group (vitamin C plus iron) and 40 into the control group (iron-only). All participants completed the 8-week follow-up, except for one in the control group who dropped out due to an unexplained intrauterine fetal death. Thus, at the 8-week follow-up, we measured the Hb and Hct levels, administered surveys, asked about adverse events, and counted the number of pills for 38 participants in the experimental group and 39 in the control group. The participants continued to take the medication until delivery, at which time we recorded the pregnancy outcomes. There was 86.8% compliance in the experimental group and 82.1% compliance in the control group.

Table 1 presents the baseline characteristics for the two groups. The mean age was 30.97 ± 8.88 years in the experimental group and 34.33 ± 7.64 years in the control group (p = 0.169). The mean BMI were 23.16 ± 3.43 kg/m^2 in the experimental group and 24.81 ± 4.19 kg/m^2 in the control group. Most participants had more than two previous pregnancies 51 (66.2%). Regarding the socioeconomic status, 70 participants (90.9%) had an income of < 25,000 baht, 71 (92.2%) had an

education level below a bachelor's degree, and 16 (20.7%) were unemployed. There were no significant differences between the two groups in terms of the baseline characteristics.

Table 1. Baseline characteristics.

Characteristic	Group		p value
	Experimental (n = 38)	Control (n = 39)	
Maternal age (years)			
mean ± standard deviation	30.97 ± 8.88	34.33 ± 7.64	0.169
Body mass index (kg/m^2)			
mean ± standard deviation	23.16 ± 3.43	24.81 ± 4.19	0.141
Serum ferritin levels (ng/ml),			
mean ± standard deviation	90.69 ± 62.61	68.07 ± 36.07	0.055
Parity			0.519
1	8 (21.1)	6 (15.4)	
2	7 (18.4)	5 (12.8)	
> 2	23(60.5)	28(71.6)	
Income			> 0.999
< 25,000 baht	35 (92.1)	35 (89.7)	
≥ 25,000 baht	3 (7.9)	4 (10.3)	
Education			0.431
Less than a bachelor's degree	34 (89.5)	37 (94.9)	
Bachelor's degree and above	4 (10.5)	2 (5.1)	
Occupation			0.081
Unemployed	11(28.9)	5 (12.8)	
Employed	27 (71.1)	34 (87.2)	

P values are from student t-test, Fisher's exact test, or the Mann–Whitney U test.

In this study, data on the participants' dietary habits were collected (Table 2), as these habits can influence iron absorption. Foods such as meat, eggs, dark leafy greens, grains, and beans are rich sources of iron, while vegetables and citrus fruits are high in vitamin C, which enhances iron absorption. Conversely, milk and coffee can inhibit iron absorption. However, no statistically significant differences in dietary intake were observed between the two groups.

Table 3 summarizes the Hb and Hct levels. The baseline Hb and Hct levels did not differ between the groups, with a mean difference of -0.11 (95% confidence interval [CI] -0.53, 0.31, p = 0.609) for Hb and -0.70 (95% CI -1.96, 0.55, p = 0.266) for Hct. At the 8-week follow-up, the mean difference in the Hb and Hct levels were not significantly different between the groups (Hb: -0.24, 95% CI: -0.67, 0.32; p = 0.253; Hct: -0.69, 95% CI -1.97, 0.58, p = 0.282). Table 4 shows the differences of changes in Hb and Hct level between the experimental and control group. The overall mean differences in Hb and Hct levels between the two groups were not significantly different after repeated measure ANOVA analysis (Hb: -0.18, 95% CI -0.55, 0.20, p = 0.350; Hct: -0.70, 95% CI -0.18, 0.42, p = 0.216).

Table 2. Dietary habits of the participants.

Dietary habit	Group		p value
	Experimental (n = 38)	Control (n = 39)	
Meat			0.409
None	0 (0.0)	0 (0.0)	
1–2 days/week	2 (5.3)	6 (15.4)	
3–4 days/week	33 (86.8)	30 (76.9)	
5–6 days/week	3 (7.9)	3 (7.7)	
Every day	0 (0.0)	0 (0.0)	
Eggs			0.050
None	0 (0.0)	0 (0.0)	
1–2 days/week	26 (68.4)	17 (43.6)	
3–4 days/week	12 (31.6)	21 (53.8)	
5–6 days/week	0 (0.0)	1 (2.6)	
Every day	0 (0.0)	0 (0.0)	
Vegetables			0.553
None	4 (10.5)	3 (7.7)	
1–2 days/week	17 (44.7)	12 (30.8)	
3–4 days/week	12 (31.6)	19 (48.7)	
5–6 days/week	3 (7.9)	4 (10.3)	
Every day	2 (5.3)	1 (2.6)	
Citrus fruit			0.508
None	7 (18.4)	8 (20.5)	
1–2 days/week	31 (81.6)	28 (71.8)	
3–4 days/week	0 (0.0)	2 (5.1)	
5–6 days/week	0 (0.0)	1 (2.6)	
Every day	0 (0.0)	0 (0.0)	
Milk			> 0.999
None	1 (2.6)	2 (5.1)	
1–2 days/week	3 (7.9)	4 (10.3)	
3–4 days/week	13 (34.2)	14 (35.9)	
5–6 days/week	18 (47.4)	17 (43.6)	
Every day	3 (7.9)	2 (5.1)	
Dark leafy greens			0.815
None	17 (44.7)	19 (48.8)	
1–2 days/week	19 (50.0)	17 (43.6)	
3–4 days/week	2 (5.3)	3 (7.7)	
5–6 days/week	0 (0.0)	0 (0.0)	
Every day	0 (0.0)	0 (0.0)	

Table 2. Dietary habits of the participants. (Cont.)

Dietary habit	Group		p value
	Experimental (n = 38)	Control (n = 39)	
Grains			0.078
None	8 (21.1)	16 (41.0)	
1–2 days/week	28 (73.7)	19 (48.7)	
3–4 days/week	2 (5.3)	4 (10.3)	
5–6 days/week	0 (0.0)	0 (0.0)	
Every day	0 (0.0)	0 (0.0)	
Beans			0.063
None	34 (89.5)	27 (69.2)	
1–2 days/week	4 (10.5)	11 (28.2)	
3–4 days/week	0 (0.0)	1 (2.6)	
5–6 days/week	0 (0.0)	0 (0.0)	
Every day	0 (0.0)	0 (0.0)	
Coffee			> 0.999
None	37 (97.4)	37 (94.9)	
1–2 days/week	1 (2.6)	1 (2.6)	
3–4 days/week	0 (0.0)	1 (2.6)	
5–6 days/week	0 (0.0)	0 (0.0)	
Every day	0 (0.0)	0 (0.0)	

Data are presented as the number (%).

P values are from Fisher's exact test.

Table 3. The hemoglobin and hematocrit levels.

Variable	Group		mean difference (95% CI)	p value
	Experimental (n = 38)	Control (n = 39)		
Initial hemoglobin, mean ± standard deviation (g/dL)	11.94 ± 0.96	12.05 ± 0.91	-0.11 (-0.53, 0.31)	0.609
Hemoglobin at 8 weeks, mean ± standard deviation (g/dL)	11.48 ± 0.95	11.73 ± 0.89	-0.24 (-0.67, 0.32)	0.253
Initial hematocrit, mean ± standard deviation (%)	36.33 ± 2.70	37.04 ± 2.83	-0.70 (-1.96, 0.55)	0.266
Hematocrit at 8 weeks, mean ± standard deviation (%)	35.10 ± 2.87	35.79 ± 2.74	-0.69 (-1.97, 0.58)	0.282

CI: confidence interval.

P values are from the Mann–Whitney U test.

Table 4. Differences of changes in Hemoglobin and Hematocrit level between the experimental and control group.

Variable	Mean difference of change between experimental and control group (95% CI for repeated-measures analysis of variance)	p value
Hemoglobin at 8 weeks VS baseline	-0.18 (-0.55, 0.20)	0.350
Hematocrit at 8 weeks VS baseline	-0.70 (-0.18, 0.42)	0.216

CI: confidence interval. P values are from the Mann–Whitney U test.

Table 5 summarizes the pregnancy outcomes. The average gestational age at delivery was 38 weeks in the experimental group and 39 weeks in the control group. The mode of delivery included vaginal delivery in 24 cases (63.2%) in the experimental group and 22 cases (56.4%) in the control group, while cesarean section rates were 14 cases (36.8%) in the experimental group and 17 cases (43.6%) in the control group. One case of postpartum hemorrhage was reported in the control group; however, no blood transfusion was required. The estimated blood loss during delivery was 243 mL in the experimental group compared to 278 mL.

Birth weights below 2,500 g were recorded in 8 cases (21.1%) in the experimental group and 3 cases (7.7%) in the control group. Apgar scores below 7 at 1 minute were observed in 33 cases (86.8%) in the experimental group and 36 cases (92.3%) in the control group, while one case (2.6%) in the experimental group had an Apgar score below 7 at 5 minutes. Neonatal intensive care unit (NICU) admissions occurred in 2 cases in each group, accounting for 5.3% in the experimental group and 5.1% in the control group. Overall, there were no significant differences between the two groups in terms of pregnancy outcomes.

Throughout the entire study treatment period, none of the participants reported any side effects from the medications and no adverse outcome occurred.

Table 5. Pregnancy outcomes of the study population between groups.

	Group		p value
	Experimental (n = 38)	**Control (n = 39)**	
Gestational age at birth (weeks)			
mean	38	39	0.922
Route of delivery, n (%)			0.556
Normal labor	24 (63.2)	22 (56.4)	
Cesarean section	14 (36.8)	17 (43.6)	
Postpartum hemorrhage, n (%)			> 0.999
Yes	0 (0.0)	1 (2.6)	
No	38 (100.0)	38 (97.4)	
Estimated blood loss (ml)			0.575
mean ± standard deviation	243 ± 102.30	278 ± 94.52	
Blood transfusion, n (%)	0 (0.0)	0 (0.0)	-
Birth weight, n (%)			0.114
< 2,500 g	8 (21.1)	3 (7.7)	
> 2,500 g	30 (78.9)	36 (92.3)	
mean ± standard deviation	2961.2 ± 340.10	3037.3 ± 393.26	
Apgar score at 1 min, n (%)			0.343
≤ 7	33 (86.8)	36 (92.3)	
> 7	5 (13.2)	3 (7.6)	
Apgar score at 5 min, n (%)			
≤ 7	1 (2.6)	0 (0.0)	
> 7	37 (97.4)	39 (100.0)	
Neonatal intensive care unit admission, n (%)	2 (5.3)	2 (5.1)	> 0.999

P values are from Fisher's exact test or the Mann–Whitney U test.

Discussion

Iron levels can significantly affect pregnancy outcomes, as iron is essential for various physiological processes, particularly the production of hemoglobin, which carries oxygen to tissues, including the placenta and developing fetus[8]. Iron deficiency anemia is a common issue in pregnant women and can lead to adverse pregnancy outcomes. The authors of a previous study reported that the prevalence of anemia increases as pregnancy progresses[8]. The prevalence gradually rises from early pregnancy (2.7%) to mid pregnancy (14.7%), and it peaks in late pregnancy (16.6%). Physiologically, in the third trimester, the velocity of the plasma volume increase slows down, which should elevate the Hb level. However, the rising prevalence of anemia in the third trimester could be attributed to inadequate iron supplementation. Several studies have identified risk factors for anemia during pregnancy[8-10]. These include age > 35 years old, multiple pregnancies, a BMI of < 18.5 kg/m², and a low educational level and income. This study selected participants without iron deficiency anemia, defined as having ferritin levels > 30 ng/mL, based on the ACOG recommendation in the inclusion criteria. However, for follow-up at 8 weeks, the ferritin levels were less useful as a follow-up marker because they were not low at baseline. Anemia during pregnancy has been linked to various pregnancy outcomes. For the prevention of iron deficiency anemia during pregnancy, many recommendations emphasize the importance of incorporating iron supplements into a pregnant woman's routine. This study chose a daily iron dose, as participants were provided with Triferdine, a supplement commonly administered daily during pregnancy and widely used among pregnant women across Thailand. However, it is important to note that iron salts are best absorbed when taken on an empty stomach[15], and studies[16] suggest that administering iron supplements every other day, rather than daily, may enhance absorption. Daily iron supplementation can stimulate the secretion of hepcidin, a hormone that regulates iron metabolism by inhibiting iron absorption in the gut[17]. This physiological response may limit the effectiveness of daily supplementation[16-17]. Therefore, while the use of Triferdine aligned with standard practice in Thailand, this approach may represent a limitation of the study, as it could have influenced the overall efficacy of the intervention.

Vitamin C is known to enhance iron absorption, and previous studies have shown that administering vitamin C alongside iron (in doses of 100–500 mg/day) to pregnant women significantly increases Hb levels without increasing the risk of adverse pregnancy outcomes[14,18,19]. This study selected a dose of 500 mg of vitamin C due to its ease of application (single tablet) and because the absolute dose of vitamin C did not appear to be associated with iron absorption or improvements in iron status[20].

This randomized controlled trial represents the first study designed to assess the effectiveness of oral iron supplementation combined with vitamin C in non-anemic pregnant women who are at risk of developing anemia—referencing the sample group from the aforementioned studies[8–10]. This study focused on prevention and treatment strategies to reduce anemia-related complications for both mothers and infants in this population. Following the intervention, the administration of vitamin C combined with iron supplements did not result in a significant increase in Hb and Hct levels. Moreover, at the 8-week follow-up, Hb and Hct levels slightly decreased in both groups despite continued treatment. These findings were consistent with those of a previous study[8] and may be attributed to physiological plasma volume expansion, inadequate nutrition, or insufficient iron supplementation. In contrast, three prior studies showed that administering vitamin C combined with iron supplements significantly increased the Hb levels[14,18,21]. This difference might be explained by the variations in sample size and population.

This study did not observe a significant reduction in adverse pregnancy outcomes among women who took vitamin C combined with iron supplements compared with the group that only took iron supplements. On the contrary, Hans et al[22] reported that a low birth weight was significantly

reduced in the group of women who received vitamin C compared to those who did not. Additionally, the group receiving vitamin C had a lower rate of hospitalization for several preventable reasons such as anemia in pregnancy, mostly iron deficient anemia (IDA) and respiratory tract infections (RTI) compared with the group that did not receive vitamin C, and the supplementation was deemed safe during pregnancy. During the entire treatment period, there were no serious adverse events. This may be attributed to the fact that we administrated only 500 mg of vitamin C per day, and most of the participants consumed low amounts of vitamin C–rich foods, such as citrus fruits, bell peppers, and tomatoes. Notably, several reports have highlighted the safety of vitamin C during pregnancy[13,23]. The tolerable upper intake level is 2,000 mg per day. Vitamin C is widely regarded as beneficial and non-toxic, with no evidence of it being carcinogen or harmful to the fetus. However, consuming more than 3,000 mg per day may lead to adverse effects, including diarrhea, nausea, vomiting, gastrointestinal discomfort, excessive iron absorption (resulting in iron overload), enamel erosion, kidney stone formation, and reduced vitamin B12 levels.

Dietary intake is a key factor that can influence iron absorption. Whole foods, fortified foods, and supplements serve as the primary sources of iron. Rich sources of heme iron include red meat, poultry, fish, and shellfish. Non-heme iron is also found in foods such as dark leafy greens, nuts, seeds, whole grains, and dried fruits. Consuming vitamin C–rich foods, like citrus fruits, bell peppers, and tomatoes, alongside non-heme iron sources can enhance iron absorption. On the other hand, drinking tea and coffee, which contain phytates, and calcium-rich beverages such as milk, consumed during meals, may reduce non-heme iron absorption[24,25]. Consequently, the findings from other studies on this topic may vary due to differences in daily dietary components, eating habits, dosage of vitamin C, types of vegetables consumed, caffeine intake, or other factors between the groups, which could have affected the interpretation of the results.

This study had several strengths. It minimized selection bias by conducting a randomized controlled trial and including all participants who had prenatal visits and met the inclusion criteria. The study followed all cases until delivery and also documented the dietary habits of each participant. However, the sample size was small, as it focused on preventing anemia in pregnant women without iron deficiency anemia. Further studies with larger sample sizes should be conducted to validate these findings.

Conclusion

This study conducted a randomized controlled trial to assess whether vitamin C and iron supplementation could prevent anemia in pregnant women at risk of developing the condition. Anemia is commonly found in pregnant women and can lead to various complications, as mentioned earlier. Identifying effective preventive measures is crucial, as anemia poses risks not only to maternal health but also to neonatal outcomes. Prevention is always preferable to treatment, as it reduces the burden on healthcare systems and improves overall pregnancy outcomes. However, this study found that administering vitamin C alongside iron did not significantly increase Hb and Hct levels compared to iron supplementation alone. The study acknowledges the limitations, which may have impacted the ability to detect subtle differences between the groups.

Potential conflicts of interest

The author declares no conflicts of interest.

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