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EDITORIAL

Intriguing Review and Topics in Sixth 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 sixth issue of Thai Journal of Obstetrics and Gynaecology 2025 contains many interesting articles. The special article is "Secondary primary cancers (SPCs) in cervical cancer survivors: A review". The contents included epidemiology, common risk factors, survival outcomes in SPCs and risk assessment and surveillance[1].

This issue also contains seven original articles. Chaipakdi performed a diagnostic study to evaluate the accuracy of an early 48–72 hours postpartum 75 g oral glucose tolerance test (75 g OGTT) for the diagnosis of diabetes mellitus (DM) at 6–12 weeks postpartum in women with gestational diabetes mellitus. The results showed an early 48–72 hours 75 g OGTT had 50% sensitivity, and 89.1% specificity for DM diagnosis. Thus, the early 48–72 hours 75 g OGTT could not replace the standard 6-12 weeks 75 g OGTT[2].

Paiboonborirak performed a retrospective study to determine the diagnostic accuracy of hemoglobin A1c (HbA1c) measured before 20 weeks' gestation as a screening tool for gestational diabetes mellitus (GDM) in high-risk pregnancies, and to evaluate whether adding HbA1c to the conventional two-step algorithm (50-g glucose-challenge [50 g GCT] test followed by the 100-gram oral glucose tolerance test [100 g OGTT]) improves early detection. The results revealed when using an HbA1c threshold of ≥ 5.7%, it provided high specificity (92.9%) and overall accuracy (81.9%) but low sensitivity (38.6%), whereas the 50-g GCT demonstrated higher sensitivity (96.5%) with lower specificity (67.6%) and accuracy (73.4%). Thus, HbA1c measured before 20 weeks in the 5.7–6.4% range could not replace glucose-based testing due to its limited sensitivity[3].

Thirunilath et al performed a prospective descriptive study detect the incidence of structural anomalies diagnosed by third trimester ultrasound after a normal anomaly scan and classify them according to major organ systems and types. They found the incidence of congenital anomalies detected in third trimester was 0.7%. Majority of them were of urogenital system (32.7%) followed by cardiovascular system (21.8%)[4].

Jirattitipat et al performed a randomized, double-blind, placebo-controlled trial to determine whether lidocaine spray at the amniocentesis puncture site, combined with oral paracetamol, reduces procedural pain compared with paracetamol alone. They found lidocaine spray combined with oral paracetamol significantly reduced pain during and immediately after the procedure, and increased maternal satisfaction[5].

Sompohnmanas et al performed a retrospective review to assess the influence of women with obesity on surgical outcomes, chemotherapy side effects, and survival rates in Thai patients with epithelial ovarian cancer. They found women with obesity with epithelial ovarian cancer was linked to an increased risk of postoperative complications, increased chemotherapy tolerability, but did not affect survival outcomes[6].

Chuchot et al performed a randomized controlled trial to determine the effectiveness of cold compression

in reducing bruising and pain around the surgical site following subdermal contraceptive implantation among female youth. They found cold compression for 5 minutes before inserting a subdermal implant and for 20 minutes three times within 24 hours was more effective in reducing bruising and pain than standard care[7].

Tachatiemchan et al performed a descriptive cross-sectional study to assess the adherence to venous thromboembolism prophylaxis and factors that influence physician decisions. The results revealed 22% received prophylaxis in accordance with the guideline. The surgical route was the only factor significantly associated with guideline adherence[8].

The Royal Thai College of Obstetricians and Gynaecologists 40th annual meeting was already held during 28 - 31 October 2025 at Dusit Thani, Pattaya, Chonburi, Thailand. The theme of the meeting is "Next Gen & Next Trend in OB-GYN". This meeting was successful with 1,300 delegates.

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SPECIAL ARTICLE

Secondary Primary Cancers in Cervical Cancer Survivors: A review

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

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

ABSTRACT

Cervical cancer (CC) continues to pose a significant global health burden, with human papillomavirus (HPV) infection, smoking, and other factors contributing to its development. Advances in CC screening, vaccination, and treatment have improved survival; however, survivors remain at considerable long-term risk of developing second primary cancers (SPCs), which are associated with substantial morbidity and mortality. Treatments such as radiation and chemotherapy, along with persistent HPV infection and lifestyle factors like tobacco use, further contribute to SPC risk. This review summarizes current evidence on SPCs in CC survivors, focusing on their epidemiology, risk factors, impact on survival, risk assessment, and surveillance strategies.

Keywords: cervical cancer, second primary cancers, second primary malignancies, survivor.

Correspondence to: *Jitti Hanprasertpong, M.D., Department of Research and Medical Innovation, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Email: hjitti@yahoo.com or hjitti@gmail.com*

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Introduction

Cervical cancer (CC) remains a leading cancer and major public health challenge for women worldwide, especially in low- and middle-income countries[1, 2]. The majority of cases arise from persistent infection with high-risk types of human papillomavirus (HPV). Additional factors—including smoking, high parity, long-term use of oral contraceptives, co-infections, immunocompromised states, and individual host susceptibility—may further increase the likelihood of developing HPV-related CC[2, 3]. Despite the availability of effective preventive measures, including CC screening (such as liquid-based cytology or HPV deoxyribonucleic acid testing), HPV vaccination, and treatment for precancerous cervical lesions, the incidence of CC has still risen significantly[4, 5]. According to the Global Cancer Statistics (GLOBOCAN) database, the age-

standardized incidence rate of CC increased from 13.3 per 100,000 in 2020 to 14.1 per 100,000 in 2022, representing an additional 58,174 cases[5]. In 2022, an estimated 662,301 new cases were reported, and if this rate persists, the global burden is projected to reach 760,082 new cases by 2030 —an increase of 14.8%[4]. Encouragingly, the number of CC survivors has continued to grow, largely due to advances in diagnostics enabling earlier detection of disease, treatment modalities, medical technology, and enhanced surveillance[6, 7]. This trend is supported by data from the GLOBOCAN database, which show that the age-standardized mortality rate for CC declined from 7.3 per 100,000 in 2020 to 7.1 per 100,000 in 2022, representing 7,043 fewer deaths[5].

CC survivors often face long-term health consequences, including disease recurrence and treatment-related complications or sequelae[7, 8], as well as an increased risk of developing new primary cancers[9-13]. With survival rates improving over the past few decades[14], increasing attention has been directed toward late-onset health complications, particularly subsequent malignant neoplasms or second primary cancers (SPCs), which are defined as new primary cancers that arise following an initial diagnosis. These SPCs are a leading cause of morbidity and nonrelapse-related mortality among CC survivors[9-13]. Multiple tumors are categorized as synchronous if they are identified at the same time or within six months of the primary tumor diagnosis and as metachronous if they are detected more than six months later[15]. Prior studies have suggested that the development of SPCs in CC survivors is influenced by several factors, including etiological factors such as HPV infection, lifestyle exposures like smoking, and treatments, particularly radiotherapy (XRT) and chemotherapy (CMT)[9-13,16-19]. Moreover, the occurrence of SPCs is linked to a significantly higher mortality risk among cervical cancer survivors compared with those without SPCs[12]. As the number of CC survivors continues to grow, so too will the burden of SPCs. This review summarizes current evidence on SPCs in CC survivors, focusing on epidemiology, risk factors, survival outcomes, risk assessment, and surveillance.

Epidemiology

With the increasing availability of epidemiologic data, evidence indicates that the incidence of SPCs among CC survivors is rising, with reported rates ranging from 5.8% to 11.0%[12, 20-22]. The most commonly affected sites are the lung, breast, stomach, colon/rectum, and female genital organs[12, 18, 21, 22]. A large population-based cohort study of 104,760 one-year CC survivors, encompassing over 1.28 million person-years of follow-up (mean 12.2 years), demonstrated a significantly elevated risk of SPCs overall (n=12,496; standardized incidence ratio [SIR]=1.30; 95% confidence interval (CI), 1.28–1.33). Increased risks were observed for HPV-related cancers (genital sites, rectum/anus, pharynx) and smoking-related cancers (lung, pharynx, bladder, pancreas) in both XRT and non-XRT groups. Importantly, excess risks of all second cancers, as well as cancers at heavily irradiated sites (colon, rectum/anus, bladder, ovary, and genital organs), were confined to women treated with XRT and persisted for more than 40 years of follow-up[11].

In 2012, a population-based study from Taiwan including 52,972 women with CC and 433,571 person-years of follow-up found that 3,061 patients (5.8%) developed SPCs. The overall risk was significantly higher than in the general population (SIR=1.36; 95% CI, 1.32–1.41), with particularly elevated risks for cancers of the lung, esophagus, stomach, small intestine, rectum, uterine corpus, vagina/vulva, bladder, kidney, bone, non-melanoma skin, and leukemia[12]. Similarly, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database reported that 6.0% (3,527/59,178) of CC survivors developed SPCs. The three most common sites of SPCs were the genital organs (20.1%), lung (18.3%), and breast (17.0%)[22].

Previous studies have reported a mean latency of 8.1 to 9.6 years between CC diagnosis and the development of SPCs[10, 12]. An analysis of the SEER

database further demonstrated a median latency of 108 months from initial CC diagnosis to SPC occurrence. The latency period varied substantially by cancer site—for example, 174 months for lung and bronchus cancers, 127 months for breast cancer, 117 months for digestive system cancers, 91 months for gynecologic cancers, and 16 months for urinary system tumors. Notably, approximately 67% of SPCs were diagnosed more than 5 years after CC onset[22].

Common risk factors

- XRT and SPCs development

XRT is a major treatment modality for CC[8, 23]. However, accumulating evidence suggests that XRT may be associated with an increased risk of developing SPCs[11, 13, 18-21]. According to the majority of previous studies, SPCs most commonly develop in the gastrointestinal system, lung, and at radiation sites (urinary bladder, genital sites, and rectum/anus)[13, 19-21]. XRT can induce SPC within the treatment field by directly damaging the DNA of healthy cells, leading to mutations and uncontrolled proliferation. Additionally, low-dose scattered radiation may cause DNA damage and generate out-of-field cancers, while systemic effects such as inflammation and immune responses may further contribute to carcinogenesis throughout the body[13, 20, 24].

Wu et al, analyzed SEER data from 23,112 CC patients, of whom 14,800 (64.0%) received XRT, using a competing-risk analysis. Overall, 2,545 patients (11.0%) developed SPCs. XRT was associated with an increased risk of second cancers in the colon, rectum, and anus (hazard ratio (HR): 1.43; 95% CI, 1.09–1.87), lung and bronchus (HR: 1.41; 95% CI, 1.13–1.76), corpus uteri (HR: 3.71; 95% CI, 1.71–8.06), ovary (HR: 2.79; 95% CI, 1.38–5.64), and urinary bladder. Conversely, radiation was associated with a significantly reduced risk of breast cancer as a second cancer (HR: 0.67; 95% CI, 0.52–0.86)[21].

- CMT and SPCs development

The most well-established association between CMT and SPCs involves therapy-related acute myeloid leukemia and myelodysplastic syndromes (t-AML/MDS). The principal chemotherapeutic agents implicated in t-AML/MDS are alkylating agents (e.g., cyclophosphamide) and topoisomerase II inhibitors (e.g., etoposide and doxorubicin)[18, 19, 25]. Karyotypic abnormalities and genetic mutations play a central role in the pathogenesis of t-AML/MDS, as they result from DNA damage induced by prior CMT[25, 26].

In a large population-based study of 60,130 women with gynecologic cancers (including cervical, endometrial, and ovarian cancers), Nasioudis et al. reported that t-AML following CMT for a gynecologic cancer was rare, with only 79 cases (0.13%), corresponding to an overall SIR of 4.41 (95% CI, 3.49–5.50). Among CC survivors, however, the risk was even higher (SIR=5.33; 95% CI, 2.92–8.95)[26]. Similarly, a population-based study from Taiwan identified carboplatin (HR: 1.58; 95% CI, 1.20–2.07) and fluorouracil (HR: 1.51; 95% CI, 1.22–1.87) as independent risk factors for developing SPCs in cervical cancer patients[18].

- HPV and SPCs development

HPV infection is the primary etiological factor in cervical carcinogenesis and has also been implicated in the development of SPMs[2, 27]. HPV-associated cancers may arise at other anatomical sites, including the vagina, vulva, anus, and oropharynx[21, 27]. Consequently, CC survivors with prior or ongoing HPV exposure remain at elevated risk of subsequent HPV-related cancers due to viral persistence, reactivation, or reinfection. Using the SEER database, Huang et al, reported elevated risks of HPV-related SPMs among CC survivors compared with the general population, regardless of XRT: SIR with XRT = 3.7 (95% CI 2.9–4.6) and without XRT = 2.7 (95% CI 2.2–3.4). The risk was higher in the XRT group, with vaginal cancer showing the greatest excess (SIR=23.8, 95% CI 14.9–36.0)[28]. In addition, a large population-based study reported increased risks of second cancers in CC patients who received XRT compared with those who did not: vulva (HR: 1.80, 95% CI 0.93–3.49), vagina (HR: 1.37, 95% CI

0.74–2.55), and oropharynx (HR: 2.02, 95% CI 0.85–4.80); however, these associations were not statistically significant[21].

- Smoking and SPCs development

HPV infection exerts a synergistic effect with cigarette smoking in cervical carcinogenesis, as smoking damages the DNA of cervical epithelial cells and impairs the immune system's capacity to clear HPV, the primary etiologic agent of cervical cancer[16, 17, 29]. Notably, CC survivors are more likely to smoke than survivors of other cancers, with nearly half (48.9%) reporting current smoking—a prevalence significantly higher than that among other cancer survivors ($p < 0.001$)[30]. This combination of elevated smoking prevalence and HPV-related susceptibility may further amplify the risk of developing tobacco-associated cancers.

An analysis of SEER data assessed the SIRs for subsequent cancers among women with an initial diagnosis of cervical, breast, or colorectal cancer. The results demonstrated that CC survivors had a markedly elevated risk of developing tobacco-associated cancers (such as lung/bronchus, pharynx, bladder, kidney, stomach, and pancreas) (SIR=2.2, 95% CI 2.0–2.4), representing roughly a twofold increase compared with breast (SIR=1.1, 95% CI 1.0–1.1) and colorectal cancer survivors (SIR=1.1, 95% CI 1.1–1.2). Notably, this excess risk was most pronounced within the first five years following the initial CC diagnosis[17].

Survival outcomes in SPCs

Population-based studies have consistently shown that SPCs substantially worsen the prognosis of CC survivors[12, 31]. Lim et al, using data from the Korea Central Cancer Registry, analyzed 72,805 women with CC and reported that 2,678 (3.68%) developed SPCs. Survival declined among patients with SPCs, with 5-year overall survival (OS) rates of 78.1% versus 83.2%, and 10-year OS rates of 65.5% versus 73.1% in the SPC and non-SPC groups, respectively[31]. A population-based study in Taiwan similarly indicated that CC patients who developed SPCs had a significantly higher mortality risk after adjusting for age, with a median survival of only 2.11 years following SPC diagnosis[12]. This worsened prognosis may be explained by the fact that SPCs often arise in previously irradiated or surgically treated regions, although unfavorable sites such as the lung are also common[11]. Management is frequently constrained by prior CC therapy, which can limit standard treatment options and reduce the feasibility of delivering adequate XRT or CMT doses or to performing extensive surgery[32].

Risk assessment and surveillance

Previous studies have demonstrated that XRT for the primary cancer is a major contributor to the risk of SPCs among CC survivors. Shared etiologies, particularly high-risk HPV infection and cigarette smoking, also play an important role[2, 17, 21, 27, 29]. Additional independent risk factors reported include older age at diagnosis, early or localized stage, race (White and Black), prior CMT, and initial surgical treatment[13, 18, 20, 22, 26]. Population-based data have been used to estimate individual SPC risk, and prediction models have been developed to support risk stratification[13, 20, 22]. Nomograms, in particular, may help identify high-risk CC survivors and guide clinicians in implementing targeted surveillance and screening strategies. However, these models are based on SEER data, which lack detailed patient information such as HPV status, smoking history, and specifics of XRT techniques or doses[13, 20, 22].

In November 2019, the Gynecologic Cancer InterGroup (GCIG) Symptom Benefit Committee convened in Athens, Greece, and emphasized incorporating cancer risks related to HPV infection and smoking into lifestyle counseling, including smoking cessation and HPV vaccination. The committee highlighted that survivors who received pelvic XRT face an elevated long-term risk of secondary pelvic cancers, even decades later, supporting the need for annual pelvic examinations. Currently, no specific follow-up guidelines exist for CC

survivors; surveillance for second cancers at other sites should follow general population guidelines to ensure equal access to routine screening services[33].

Conclusion

CC continues to pose a significant worldwide health issue, with HPV infection, smoking, and other factors contributing to its development. Advances in screening, HPV vaccination, and treatment have improved survival, yet many CC survivors continue to face a substantial long-term risk of developing SPCs. Key contributors include XRT, CMT, persistent HPV infection, and tobacco use. The presence of SPCs is associated with poorer survival outcomes compared with CC alone. Prediction models and nomograms may help in identifying high-risk CC survivors and guiding targeted surveillance, though their accuracy is limited by incomplete patient data. Lifestyle counseling on HPV and smoking, together with annual pelvic examinations for CC survivors who received pelvic XRT—even decades later—is highly recommended. For other cancers, follow-up should follow general population standards. Proactive risk assessment and individualized monitoring are essential to improving long-term outcomes for CC survivors.

Potential conflicts of interest

The authors declare no competing interests.

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OBSTETRICS

Accuracy of 48-72 Hours Postpartum 75g Oral Glucose Tolerance Test for Diagnosis of Postpartum Diabetes Mellitus in Gestational Diabetes Mellitus

Pakprapa Chaipakdi, M.D.*

** Department of Obstetrics and Gynecology, Hatyai Hospital, Hatyai, Songkhla, Thailand*

ABSTRACT

Objectives: This study aimed to evaluate the accuracy of an early 48–72 hours postpartum 75 g oral glucose tolerance test (OGTT) for the diagnosis of diabetes mellitus (DM) at 6–12 weeks postpartum in women with gestational diabetes mellitus (GDM).

Materials and Methods: This diagnostic study included 100 women with GDM who delivered at Hatyai Hospital between January and July 2024. Participants underwent a 48–72-hour postpartum 75 g OGTT and repeated the test at 6–12 weeks. Early results were compared with the standard 6–12-week test. Outcomes included sensitivity, specificity, accuracy, predictive values, and ROC analysis of the early postpartum OGTT for diagnosing DM.

Results: The 48–72-hour postpartum 75 g OGTT showed 79.3% sensitivity and 53.6% specificity for diagnosis of postpartum glucose intolerance. For DM diagnosis, it had 50% sensitivity, 89.1% specificity, and 98.6% negative predictive value. Receiver operating characteristic analysis of the early 2-hour post-OGTT identified a cut-off >182 mg/dl, with 90.0% sensitivity and 82.0% specificity for diagnosis of DM.

Conclusion: Although the early 48–72 hours 75 g OGTT cannot replace the standard 6–12 weeks 75 g OGTT, it is useful in identifying high-risk patients who require follow-up and in raising awareness to return for routine postpartum checkups. Additionally, the early 2-hour post-OGTT may be considered as an aid in the diagnosis of DM.

Keywords: accuracy, postpartum 75g oral glucose tolerance test, diabetes mellitus, gestational diabetes mellitus.

Correspondence to: *Pakprapa Chaipakdi, M.D., Department of Obstetrics and Gynecology, Hatyai Hospital, Hatyai, Songkhla, Thailand.* ***E-mail: gwangmed29@hotmail.com***

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ความแม่นยำของการตรวจคัดกรองเบาหวานโดยการกินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง ในการวินิจฉัยโรคเบาหวานหลังคลอดในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์

พักตร์ประภา ไชยภักดี

บทคัดย่อ

วัตถุประสงค์: *หาความแม่นยำของการตรวจคัดกรองเบาหวานโดยการกินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง ในการวินิจฉัยโรคเบาหวานหลังคลอดในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบทดสอบวินิจฉัยความแม่นยำที่ทำในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์และคลอด ณ โรงพยาบาลหาดใหญ่จำนวน 100 คน ตั้งแต่เดือนมกราคมถึงเดือนกรกฎาคม พ.ศ.2567 โดยการตรวจคัดกรองเบาหวานให้กินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง เทียบกับหลังคลอด 6-12 สัปดาห์ เพื่อวินิจฉัยโรคเบาหวานหลังคลอด โดยวิเคราะห์เป็น ความไว ความจำเพาะ ความแม่นยำ ค่าทำนายผลบวก ค่าทำนายผลลบ และการวิเคราะห์เส้นโค้งหาจุดตัดที่เหมาะสม*

ผลการศึกษา: *การตรวจคัดกรองเบาหวานโดยการกินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง มีความไวค่อนข้างดีคือ 79.3 เปอร์เซ็นต์ แต่มีความจำเพาะอยู่ในระดับปานกลางคือ 53.6 เปอร์เซ็นต์ ในการวินิจฉัยภาวะพร่องความทนทานต่อน้ำตาลหลังคลอด แต่อย่างไรก็ตามการตรวจคัดกรองเบาหวานหลังคลอด 48-72 ชั่วโมงนี้ก็มีความจำเพาะและค่าทำนายผลลบสูง (89.1 และ 98.6 เปอร์เซ็นต์ตามลำดับ) แม้จะมีความไวระดับปานกลาง (50 เปอร์เซ็นต์) ในการวินิจฉัยโรคเบาหวาน เมื่อวิเคราะห์เส้นโค้งหาจุดตัดที่เหมาะสมของค่าระดับน้ำตาลพบว่าถ้าค่าระดับน้ำตาลหลังกินน้ำตาล 75 กรัม 2 ชั่วโมงหลังคลอด 48-72 ชั่วโมงมากกว่า 182 มิลลิกรัมต่อเดซิลิตร จะมีความไวและความจำเพาะค่อนข้างสูง (90.0 และ 82.0 เปอร์เซ็นต์ ตามลำดับ)ในการวินิจฉัยโรคเบาหวานหลังคลอด*

สรุป: *แม้ว่าการตรวจคัดกรองเบาหวานโดยการกินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง จะไม่สามารถใช้แทนการคัดกรองเบาหวานตามมาตรฐานที่ทำในช่วงหลังคลอด 6-12 สัปดาห์ เพื่อวินิจฉัยโรคเบาหวานได้ อย่างไรก็ตามการตรวจคัดกรองเบาหวานหลังคลอด 48-72 ชั่วโมงนี้ก็มีประโยชน์ในการคัดกรองสตรีที่มีโอกาสจะมีภาวะพร่องความทนทานต่อน้ำตาลที่จำเป็นต้องได้รับการตรวจยืนยันภาวะเบาหวานอีกครั้งหลังคลอด นอกจากนี้พบว่าค่าระดับน้ำตาล 2 ชั่วโมง หลังกินน้ำตาล 75 กรัม หลังคลอด 48-72 ชั่วโมง ที่มากกว่า 182 มิลลิกรัมต่อเดซิลิตร อาจจะช่วยวินิจฉัยโรคเบาหวานหลังคลอดได้*

คำสำคัญ: *ความแม่นยำ, การตรวจคัดกรองเบาหวานโดยการกินน้ำตาล 75 กรัม, โรคเบาหวาน, ภาวะเบาหวานขณะตั้งครรภ์*

Introduction

Gestational diabetes (GDM) is defined as diabetes diagnosed during pregnancy that is not overt diabetes and usually resolves 6-12 weeks after delivery. GDM is the most common cause of both maternal and neonatal complications, affecting about 6% of pregnancies[1-4]. GDM can be classified as either GDM type A1 (non-insulin-dependent) or GDM type A2 (insulin-dependent[5]. If the glycemic target is not achieved (fasting blood glucose target is < 95 mg/dl, 2 hours postprandial glucose target is < 120 mg/dl), the patients receive insulin treatment. Individuals with history of GDM have a greatly increased risk of 50% of developing type 2 diabetes mellitus (DM) within 10 years[6]. DM can be classified as either type 1 DM (insulin deficiency due to β-cell destruction) or type 2 DM (increased insulin resistance). Thus, the American Diabetes Association (ADA 2023)[7] recommends a 75g oral glucose tolerance test (OGTT) 4-12 weeks postpartum to screen for type 2 DM, a positive screen for DM requires two abnormal values: fasting blood glucose (FBG ≥ 126 mg/dl) and 2-hour plasma glucose ≥ 200 mg/dl. If only one abnormal value in the OGTT meets the DM criteria, the test should be repeated to confirm that the abnormality persists. Unfortunately, less than 50% of women with GDM received 75g OGTT postpartum screening due to loss of follow-up in the previous studies[8, 9].

Some studies showed early postpartum OGTT had a high sensitivity and specificity when compared with the 6-12 weeks postpartum test due to the level of placenta insulin resistance hormone in pregnancy declining quickly after delivery[10, 11], placental hormones decrease abruptly and return to prepregnancy levels within a few days to weeks. While the majority of women return to their prepregnancy glycemic status almost immediately, several women with GDM may have previously unrecognized type 2 DM. Therefore, the Endocrine Society recommends checking fasting or random blood glucose 24–72 hours after delivery to exclude persistent hyperglycemia or overt DM. The early postpartum 75 g OGTT offers several benefits, including improving follow-up rates for postpartum screening, enabling earlier detection, and facilitating counseling and management of women with early postpartum glucose intolerance or type 2 DM. However, studies in Thailand remain limited. Therefore, this study evaluated the accuracy of early postpartum 75 g OGTT in diagnosing postpartum DM among women with GDM at Hatyai Hospital.

Materials and Methods

This study utilized a diagnostic test. Approval for this research was received by the Institutional Review Board of Hatyai Hospital (IRB:HYH-EC 098-66-01) on December 19, 2023. The study population included 100 women who were diagnosed with GDM by early or routine two-step screening and who delivered babies at Hatyai Hospital between January and July 2024. Women with pre-gestational diabetes or a history of glucose metabolism affected by drug usage were excluded.

Based on the postpartum 2-hour 75 g OGTT, the ADA 2003 criteria[12] were used to define impaired fasting glucose (FBG 110–125 mg/dL), impaired glucose tolerance (2-hour post-OGTT 140–199 mg/dL), and DM (FBG ≥ 126 mg/dL or 2-hour post-OGTT ≥ 200 mg/dL). Both impaired glucose regulation and DM can be referred to as "glucose intolerance"[13].

The sample size was calculated by the prevalence of postpartum glucose intolerance women based on a previous study[13]. Sensitivity and specificity were accepted following the study by Bhalli[11]. This estimate required 82 cases, augmented by 20% to account for dropouts, resulting in a total of 100 cases to achieve 80% power at a 95% confidence interval.

After informed consent was gained, all patients were advised according to the institutional

guidelines. None of the patients withdrew from the study, and all stated they were breastfeeding during their hospital stay. Consenting patients underwent a 2-hour 75 g OGTT 48–72 hours postpartum, including early FBG and the early 2-hour post-OGTT before hospital discharge. This test was repeated 6-12 weeks postpartum at a nearby hospital. The patients were instructed not to eat anything at least 8 hours before FBG was checked and until 2 hours after blood glucose, after 75g glucose intake was checked completely. If the first 75g OGTT was abnormal, the patients were advised by the attending doctor to make lifestyle and dietary modifications involving healthy eating, calorie restriction, regular exercise, limiting alcohol, and stopping smoking, etc. They also needed to return for a routine follow-up 6-12 weeks postpartum for the 75g OGTT. If the 75g OGTT was abnormal 6-12 weeks postpartum, the patients were referred to the endocrinology outpatient clinic.

Women were reminded to return for further testing at 6-12 weeks postpartum by phone calls weekly between 5-10 weeks postpartum. Medical records were obtained from Hatyai Hospital or from the primary doctors at other accredited hospitals where the patients attended postpartum follow-up.

The collected data included demographic data, antepartum, delivery records, family history, and postpartum 75g OGTT results. The primary outcome was the accuracy of 48-72 hours postpartum 75g oral glucose tolerance test for diagnosing postpartum diabetes mellitus using the 6-12 weeks routine postpartum 75g OGTT as the gold standard for gestational diabetes mellitus.

Statistical analysis was done by the R program (version 4.4.1) Sensitivity, specificity, accuracy positive (PPV), and negative predictive value (NPV) were calculated to predict glucose intolerance, and p values < 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were illustrated, the area under the curve (AUC) with 95% confidence interval (CI) was reported to determine the sensitivity, specificity at difference cut-off values.

Results

Among 100 cases of pregnancy with GDM who completed an early postpartum test, with 15 lost to follow-up for 6-12 weeks postpartum test, most were found to be non-insulin-dependent GDM (77%). A previous history of GDM was revealed in about 8%. Additionally, they had a previous family history of DM at up to 34%. The mean age of patients was 30 ± 6.21 years, and the median pre-pregnancy body mass index (BMI) was 26 kg/m^2; about 23% of the patients were obese (pre-pregnancy BMI ≥ 30 kg/m^2). Most of the patients (about 69%) were multigravida, two cases were twin pregnancy and one of them lost to follow-up 6 weeks postpartum. The median of the GDM-diagnosed gestational age was 25 weeks. The median time between delivery to early postpartum and 6-12 weeks postpartum test was 54 hours and 6.3 weeks, respectively. None of the patients received anti-glycemic drugs. The modes of delivery included vaginal delivery (56%) and cesarean section (CS) (44%); none underwent operative vaginal delivery. The median birthweight was 3,140 grams. Data are shown in Table 1.

The mean of FBG at 48-72 hours postpartum was significantly less than at 6-12 weeks postpartum OGTT (77.61 and 90.92 mg/dl, respectively, $p < 0.001$). However, the mean glucose levels were significantly higher after 2 hours of 75 g OGTT at 48-72 hours postpartum than at 6-12 weeks postpartum OGTT (147.29 and 129.05 mg/dl, respectively, $p < 0.001$). Data are shown in Table 2.

The proportion of diabetic patients at 48–72 hours postpartum and at 6–12 weeks postpartum was 11.76% and 2.35%, respectively. The proportion of the impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) groups at 48–72 hours postpartum and at 6–12 weeks postpartum was 45.88% and 31.76%, respectively. Data are shown in Fig. 1.

Table 1. Demographic and obstetric data for the studied patients (n = 100).

Characteristics	N (%)
Age (years), mean (SD)	30 (6.21)
Gravida	
Primi	31 (31.00)
Multi	69 (69.00)
Pre-pregnancy BMI (kg/m^2), median (IQR)	26 (23.05-29.83)
Pre-pregnancy BMI ≥ 30 kg/m^2	23 (23.00)
GA at first GDM diagnosis (weeks), median (IQR)	25 (15.75-27.00)
Family history of DM	34 (34.00)
Previous history of GDM	8 (8.00)
Type of GDM	
non-insulin-dependent GDM	77 (77.00)
insulin-dependent GDM	23 (23.00)
Route of delivery	
NL	56 (56.00)
CS	44 (44.00)
Birthweight (grams), median (IQR)	3,140 (2,819-3,412)
Postpartum test (hours), median (IQR)	54 (48.00-64.00)
Postpartum (weeks), median (IQR)	6.30 (6.00-6.90)

SD: standard deviation, IQR: in quartile range, BMI: body mass index, GA: gestational age, GDM: gestational diabetes, NL: normal labor, CS: Cesarean section

Table 2. Comparison of blood glucose levels between 48-72 hours and 6-12 weeks postpartum 75g OGTT.

Glucose test	At 48-72 hrs (n = 85) mean (SD)	At 6 wks (n = 85) mean (SD)	mean difference mean (SD)	p value*
FBG (mg/dl)	77.61 (11.27)	90.92 (8.58)	13.31 (12.85)	< 0.001
2-hr post OGTT (mg/dl)	147.29 (42.01)	129.05 (32.70)	18.25 (41.22)	< 0.001

Values are given as mean (SD: standard deviation), FBS: fasting blood glucose, OGTT: oral glucose tolerance test, * pair t- test 2 tail

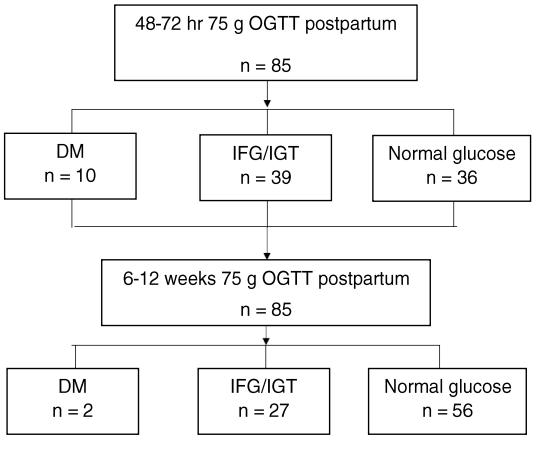

Fig. 1. The number of patients with diabetes mellitus (DM), impaired fasting glucose (IFG) /impaired glucose tolerance (IGT), and normal glucose at the early 48–72 hours oral glucose tolerance test (OGTT) and at 6–12 weeks postpartum (n = 85).

A total of 6 cases with normal 75g OGTT at 48-72 hours postpartum had impairment (IFG/IGT) 6-12 weeks later. None of the women with normal 75g OGTT at 48-72 hours postpartum had DM at 6-12 weeks postpartum. One of 39 women who were impaired at 48-72 hours postpartum had DM at 6-12 weeks postpartum. Of the 10 women who tested positive for DM early postpartum, 60% had either impairment or DM at 6-12 weeks postpartum. Overall, 8.2% of women (n = 7) had a change in 75g OGTT results at 6-12 weeks from normal to impaired (n = 6) or a change from impaired to DM (n = 1), and no case change from normal to DM. Therefore, the study had false negative results of about 16.7%. Additionally, 36.5% (n = 31) had a change in 75 g OGTT results at 6–12 weeks from impaired to normal (n = 22), a change from DM to normal (n = 4), and a change from DM to impaired (n = 5), while 55.3% (n = 47) had the same results between the early 75 g OGTT and 6–12 weeks postpartum. Data are shown in Table 3.

The sensitivity of early 48-72 hours postpartum 75g OGTT was 50% for diagnosing DM and 79.3% for diagnosing impaired or DM results with a PPV of 10% and 46.9%, respectively.

The specificity was 89.1% for DM and 53.6% for impaired or DM results with an NPV of 98.6 % and 83.3%, respectively. Data are shown in Table 4

Table 3. The data of patients with prediabetes and diabetes status at the early 48–72-hour OGTT and at 6–12 weeks postpartum.

Early 75g OGTT	Postpartum 6-12 weeks, 75g OGTT			
	Normal	IFG/IGT	DM	Total
Normal	30 (83.33%)	6 (16.67%)	0 (0.00%)	36
IFG/IGT	22 (56.41%)	16 (41.03%)	1 (2.56%)	39
DM	4 (40.00%)	5 (50.00%)	1 (10.00%)	10
Total	56	27	2	85

OGTT: oral glucose tolerance test, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, DM: diabetes

Table 4. Accuracy of early 48-72 hours 75g OGTT postpartum for predicting 6 -12 weeks postpartum glucose intolerance.

Status at 6 wks post-partum	Early 48-72 hrs. 75g OGTT	Number of disease	Number of non- disease	Sensitivity % (95%CI)	Specificity % (95%CI)	Accuracy % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
DM (n=2)	Abnormal	1	9	50.00	89.15	88.24	10.00	98.67
	Normal	1	74	(9.45, 90.55)	(80.66, 94.19)	(79.68, 93.48)	(1.79, 40.42)	(92.83, 99.76)
Impaired or DM (n=29)	Abnormal	23	26	79.31	53.57	62.35	46.94	83.33
	Normal	6	30	(61.61, 90.15)	(40.70, 65.98)	(51.73, 71.91)	(33.70, 60.61)	(68.11, 92.13)

Values are given as a number, sensitivity, specificity, accuracy, PPV: positive predictive value and NPV: negative predictive value
OGTT: oral glucose tolerance test, DM: diabetes, CI: confidence interval

The ROC curve was constructed for early 48-72-hour postpartum 75 g OGTT and the results of the 6-12-week postpartum OGTT (Fig. 2). ROC analysis of early FBG indicated an AUC of 0.64 (95%CI, 0.51-0.76) for prediabetes (IFG or IGT), as well as an AUC of 0.53 (95%CI, 0.33-0.73) for the DM. Both conditions failed to diagnose prediabetes and the DM. With regard to the early 2-hr post OGTT, AUC was 0.74 for diagnoses (95%CI, 0.63-0.86) of prediabetes, and AUC was 0.90 (95%CI, 0.76-1.00) for the DM. The early 2-hr post OGTT was considered optimal for separating the patients. The cut-off value determined by the ROC for the prediabetes by early 2-hr post OGTT was more than 145 mg/dl with a sensitivity of

78% and a specificity of 64%. Furthermore, the cut-off value for diagnosing the DM was more than 182 mg/dl for the early 2-hr post OGTT with a sensitivity of 90% and a specificity of 82%.

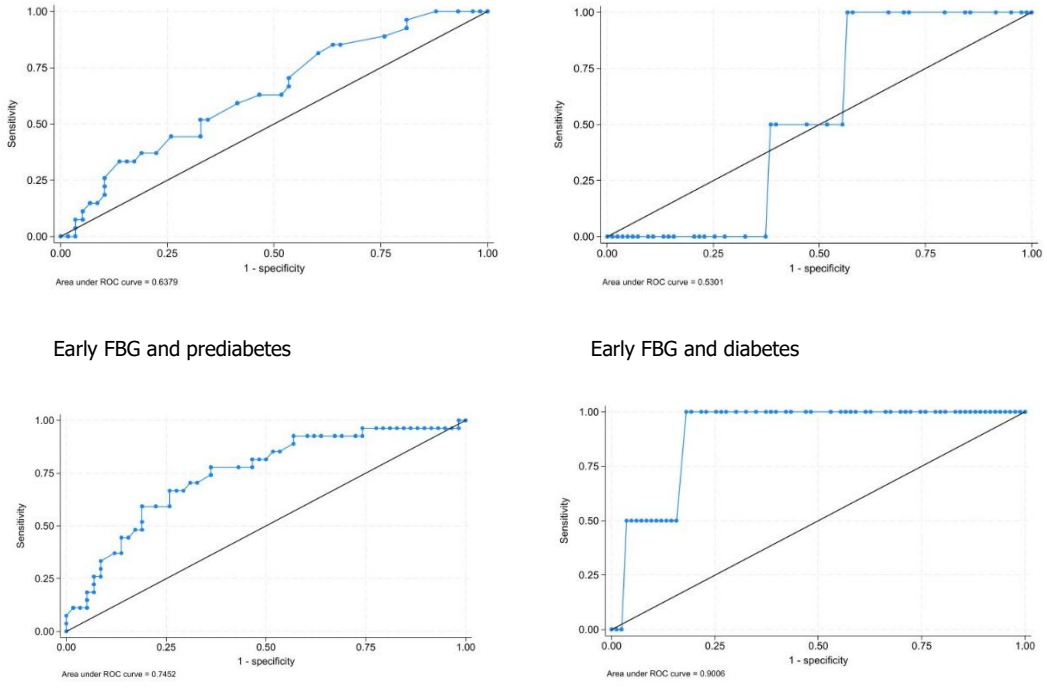

Fig. 2. Receiver operating characteristic curve for early 48-72 hours fasting blood glucose (FBG) and 2- hours glucose levels and the results of 6-12 weeks of 75 g oral glucose tolerance test (OGTT).

Discussion

GDM is the most common cause of both maternal and neonatal complications and increases the risk by 50% of developing type 2 DM. Therefore, the ADA 2023 recommends routine 75g OGTT 4-12 weeks postpartum. However, nearly 50% of women drop out. Some studies showed early postpartum OGTT had a high sensitivity and specificity when compared with the 6-12 weeks postpartum test[14-19], therefore the present study was focused on the accuracy of early postpartum 75g OGTT to detect postpartum DM.

This study found that among 100 cases of women who completed early 48-72 postpartum hours 75g OGTT, only 85 cases followed-up with the 6-12 weeks postpartum test. The proportion of DM in early and 6-12 weeks postpartum was 11.76% and 2.35%, respectively. This study showed that the mean of FBG at 48-72 hours postpartum was significantly less than at 6-12 weeks postpartum OGTT (77.61 and 90.92 mg/dl, respectively, $p < 0.001$). It could be explained that the women experienced prolonged fasting during labor, especially in the cesarean section group, who were required to fast for at least 8 hours before the operation and 24 hours post-operation until resuming diet, according to Hatyai Hospital protocol. This may have contributed to the low FBG. However, the mean glucose levels after 2-hr 75 g OGTT at 48-72 hours postpartum was significantly higher than those observed at 6-12 weeks postpartum (147.29 and 129.05 mg/dl, respectively, $p < 0.001$) (Table 2). This could be explained by the level of placental insulin resistance hormone in pregnancy declining rapidly after delivery and reached pre-pregnancy level within a few days to weeks. Therefore, the mean glucose levels at 6–12 weeks postpartum were lower than

those in the early postpartum period[11].

This study showed that early 48-72-hour postpartum 75g OGTT after delivery carried an impressive sensitivity (79.3 %) but a modest specificity (53.6%) for detecting glucose intolerance (impaired or DM) with a PPV of 46.9%, similar to the study by Water et al[14]. In addition, this study found that the high specificity (89.1%) but modest sensitivity (50%) for detect DM were similar to studies by Water et al and Carter et al[14, 9]. However, this study was not correlated with the study by Werner et al[8], which reported a higher sensitivity (100%) and specificity (94%) for detect DM. This may be due to the difference in timing of early 75 g OGTT; their early test was undertaken in the morning of postpartum day 2, while the test in this study was undertaken at 48-72 hours postpartum. It may be explained by the physiological change of the placental hormone declining quickly and maintaining 48-72 hours after delivery, which was related to the initial timing of the early test and could have had an impact on both sensitivity and specificity. Moreover, the study by Werner et al[8] involving a lot of women who were lost to follow-up (50%) when compared with our study, which had just 15% lost.

The study by Aghdam et al[15] likewise was found to have results with higher sensitivity and specificity (82.14% and 70.89%, respectively) than our study (79.31% and 53.57%, respectively), which may be due to the difference in population. Most of the population in the Aghdam et al's study had severe diabetes, while those in the current study had mild diabetes.

The current study found that the prevalence of postpartum diabetes (2.35%) was lower than in many other studies[11, 15], which might explain the lower positive predictive value (10%) of early postpartum 75 gOGTT for predicting postpartum diabetes. A total of 6 cases (16.67%) with normal results were observed in the early test, but abnormal results (impaired group) in 6-12 weeks postpartum, which was considered a false negative result. This was possibly due to long fasting during labor or postcesarean as well as poor nutrition during hospitalization. None of the women with normal 75g OGTT at 48-72 hours postpartum had DM at 6-12 weeks postpartum (NPV 100%). Therefore, if the patients had negative results on the early test, this test could be used for counseling to reduce the anxiety levels of patients about turning to postpartum DM, and it could be helpful for excluding permanent hyperglycemia or unrecognized DM. Although early 48-72-hour 75 g OGTT cannot replace the routine 6-12 weeks 75 g OGTT, it is useful in identifying high-risk patients who need to follow-up and have the awareness to return for routine postpartum check up. With regard to the early 2-hr post OGTT, AUC showed diagnoses of 0.74 and 0.90 for prediabetes and diabetes, respectively, which was diagnosed at 6-12 weeks postpartum OGTT. ROC analysis of the 2-hour post-OGTT identified a cut-off > 182 mg/dl, with 90.0% sensitivity and 82.0% specificity for diagnosis of DM. Therefore, the early 2-hr post OGTT could be considered optimal for separating prediabetes and diabetes from normal patients. Another benefit of this study is its usefulness in encouraging patients with abnormal results to modify their lifestyles and behavior patterns to decrease the risk of DM in the future.

A strength of this study was that there were more patients that nearly completed routine follow-up with the 6-12 weeks postpartum test (85%) than in previous studies. This research is one of the few studies in Thailand that assess the use of early postpartum 75 g OGTT to diagnose postpartum DM in women with GDM.

There were some limitations in this study. This research utilized a relatively small sample size, which reduced the statistical power and generalizability of the findings, and conducted in a single-center study, which limited the external validity of the results. Therefore, the results from this study should be interpreted with caution when using the 75 g OGTT at 48–72 hours postpartum to diagnose DM in women with GDM, as the findings may not represent the

general population and might be subject to bias.

In a recent study, the 1-hour 75 g OGTT performed equally well or better than the 2-hour OGTT in predicting type II DM[20]. We suggest that future studies adopt a multicenter design and incorporate additional tests, such as the 1-hour OGTT, to improve the prediction of DM.

Conclusion

Although the early 48–72 hours 75 g OGTT cannot replace the standard 6–12 weeks 75 g OGTT, it is useful for identifying high-risk patients who require follow-up and for raising awareness to return for routine postpartum checkups. Additionally, the early 2-hour post-OGTT may be considered as an aid in the diagnosis of DM.

Potential conflicts of interest

The authors declares no conflicts of interest.

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OBSTETRICS

Accuracy of HbA1c Levels as a Screening Tool for Gestational Diabetes Mellitus in Pregnant Women Prior to 20 Weeks of Gestation

Chaiyawut Paiboonborirak, M.D.*

** Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration General Hospital, Bangkok Metropolitan Administration, Bangkok, Thailand*

ABSTRACT

Objectives: To determine the diagnostic accuracy of hemoglobin A1c (HbA1c) measured before 20 weeks' gestation as a screening tool for gestational diabetes mellitus (GDM) in high-risk pregnancies, and to evaluate whether adding HbA1c to the conventional two-step algorithm (50-g glucose-challenge [50 g GCT] test followed by the 100-gram oral glucose tolerance test [100 g OGTT]) improves early detection.

Materials and Methods: This retrospective study included 282 pregnant women who met high-risk criteria for GDM. All participants underwent HbA1c measurement and a 50 g GCT at the first antenatal visit. Elevated HbA1c levels (≥ 5.7%) and/or abnormal GCT results (≥ 140 mg/dL) prompted patients to undergo a diagnostic 100g OGTT. Receiver operating characteristic curve analysis was used to identify the optimal HbA1c cutoff and to calculate sensitivity, specificity, PPV, NPV and accuracy. The screening performance of HbA1c was compared with 50 g GCT.

Results: Among 282 high-risk pregnancies, the overall prevalence of GDM was 29.8% (84/282), and 20.2% (57/282) were diagnosed before 20 weeks of gestation. Women with early-pregnancy HbA1c levels of 5.7–6.4% (38/282, 13.5%) had a significantly higher prevalence of GDM compared with those with HbA1c < 5.7% (71.1% vs 23.4%, respectively) and were more likely to require insulin therapy (13.2% vs 1.6%, $p < 0.001$). ROC analysis for HbA1c yielded an area under the curve of 0.716. Using an HbA1c threshold of ≥ 5.7% provided high specificity (92.9%) and overall accuracy (81.9%) but low sensitivity (38.6%), whereas the 50-g GCT demonstrated higher sensitivity (96.5%) with lower specificity (67.6%) and accuracy (73.4%).

Conclusion: HbA1c measured before 20 weeks in the 5.7–6.4% range could not replace glucose-based testing due to its limited sensitivity. However, with high specificity and an overall accuracy of 81.9%, it served as a valuable adjunct to the 50 g GCT within the two-step screening protocol, especially in cases where glucose loading was intolerant.

Keywords: hemoglobin A1c, early screening, gestational diabetes mellitus, 50-g glucose challenge test, oral glucose tolerance test

Correspondence to: *Chaiyawut Paiboonborirak, M.D., Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration General Hospital, Bangkok Metropolitan administration, Bangkok 10100, Thailand. E-mail: isletken@gmail.com*

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ความแม่นยำของระดับฮีโมโกลบินเอวันซี (HbA1c) ในการเป็นเครื่องมือคัดกรองภาวะเบาหวานขณะตั้งครรภ์ก่อนอายุครรภ์ 20 สัปดาห์

ชัยวุฒ ไพบูลย์บริรักษ์

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินความถูกต้องของการวัดระดับฮีโมโกลบินเอวันซี (HbA1c) ก่อนอายุครรภ์ 20 สัปดาห์ ในการคัดกรองภาวะเบาหวานขณะตั้งครรภ์ในสตรีกลุ่มเสี่ยงสูง และเสนอแนวทาง "HbA1c-first" ในกระบวนการตรวจคัดกรอง*

วัสดุและวิธีการ*: การศึกษาย้อนหลัง (retrospective cohort) ดำเนินการที่โรงพยาบาลกลาง สำนักการแพทย์ กรุงเทพมหานคร โดยคัดเลือกสตรีตั้งครรภ์ จำนวน 282 ราย (อายุ 18–45 ปี อายุครรภ์น้อยกว่า 20 สัปดาห์) ซึ่งมีปัจจัยเสี่ยงสูงต่อภาวะเบาหวานขณะตั้งครรภ์ ผู้เข้าร่วมได้รับการเจาะเลือดตรวจระดับ HbA1c และทดสอบ 50-g glucose challenge test (50g GCT) ในการฝากครรภ์ครั้งแรก หากผล 50g GCT ผิดปกติ (≥140 มก./ดล.) จะได้รับการตรวจยืนยันด้วยการทดสอบ 100-g oral glucose tolerance test (100g OGTT) ในกรณีที่พบ HbA1c ≥ ร้อยละ 6.5 ให้การวินิจฉัยเป็นเบาหวาน และส่งปรึกษาแพทย์ผู้เชี่ยวชาญ วิเคราะห์สมรรถนะของจุดตัด HbA1c ต่าง ๆ ด้วย receiver operating characteristic (ROC) เพื่อประเมินความไว ความจำเพาะ ค่าทำนายบวก และค่าทำนายลบ*

ผลการศึกษา*: พบอุบัติการณ์ของภาวะเบาหวานขณะตั้งครรภ์ ร้อยละ 29.8 โดยร้อยละ 20.2 ได้รับการวินิจฉัยก่อนอายุครรภ์ 20 สัปดาห์ กลุ่มที่มี HbA1c ร้อยละ 5.7–6.4 พบอัตราการเกิดภาวะเบาหวานขณะตั้งครรภ์สูงกว่ากลุ่ม HbA1c < ร้อยละ 5.7 อย่างมีนัยสำคัญ (ร้อยละ 71.1 เทียบกับร้อยละ 23.4, p < 0.001) และต้องใช้อินซูลินมากกว่า (ร้อยละ 13.2 เทียบกับร้อยละ 1.6, p < 0.001) การวิเคราะห์ ROC ให้ค่า area under the curve เท่ากับ 0.716 บ่งชี้ความแม่นยำที่ยอมรับได้ เมื่อใช้จุดตัด HbA1c ≥ ร้อยละ 5.7 ให้ความจำเพาะสูง (ร้อยละ 92.9) แต่ความไวต่ำ (ร้อยละ 38.6)*

สรุป*: การใช้ HbA1c ในช่วงร้อยละ 5.7–6.4 ตั้งแต่ก่อนอายุครรภ์ 20 สัปดาห์ มีประสิทธิภาพในการระบุกลุ่มเสี่ยงสูงที่ควรเข้ารับการตรวจยืนยันด้วย 50g GCT และ 100g OGTT ก่อนกำหนด ในทางกลับกัน หาก HbA1c ต่ำกว่าร้อยละ 5.7 อาจเลื่อนการตรวจแบบสองขั้นตอน ไปจนถึงช่วง 24–28 สัปดาห์ได้ แม้ว่าจะไม่สามารถใช้ HbA1c ทดแทนการประเมินระดับน้ำตาลด้วยกลูโคสได้ทั้งหมด แต่ด้วยความจำเพาะที่สูงจึงสามารถใช้เป็นเครื่องมือเสริมที่ช่วยเพิ่มประสิทธิภาพในการคัดกรองภาวะเบาหวานขณะตั้งครรภ์ได้เป็นอย่างดี*

คำสำคัญ*: ฮีโมโกลบินเอวันซี (HbA1c), การคัดกรองระยะแรก, เบาหวานขณะตั้งครรภ์, การทดสอบกลูโคส 50 กรัม (50-g GCT), การทดสอบกลูโคส 100 กรัม (OGTT)*

Introduction

Gestational diabetes mellitus is a significant pregnancy-related disorder that profoundly impacts maternal and fetal outcomes. Women diagnosed with GDM are more likely to develop type 2 diabetes mellitus (T2DM) later in life and face elevated risks of hypertensive disorders and preeclampsia[1]. Additionally, GDM is associated with adverse neonatal outcomes, including fetal macrosomia, birth trauma (e.g., brachial plexus injury and clavicular fractures), stillbirth, and neonatal hypoglycemia[2,3]. Children born to mothers with GDM are also more susceptible to obesity and metabolic diseases, such as T2DM[4]. Moreover, GDM increases healthcare utilization, underscoring the importance of accurate, early screening to mitigate potential adverse outcomes[5].

Currently, 6–8% of pregnant women are affected by GDM, a figure that rises to 7–14% among those with obesity[6]. Approximately 90% of these cases are first identified during pregnancy or at the initial antenatal visit[5,6]. GDM is defined as diabetes that is first diagnosed during pregnancy and includes both "true" gestational diabetes and previously undiagnosed pregestational diabetes[7]. This condition elevates risks for macrosomia, birth trauma, stillbirth, preeclampsia, increased cesarean delivery rates, and neonatal hypoglycemia[7, 8]. Consequently, early identification and effective management are paramount to safeguarding maternal and neonatal well-being.

Two principal approaches for diagnosing GDM currently exist: the one-step and the two-step methods. The two-step approach, recommended by the American College of Obstetricians and Gynecologists (ACOG), includes an initial 50g glucose challenge test (50g GCT) at 24–28 weeks, followed by a 100g oral glucose tolerance test (100g OGTT) if the 50g GCT result is abnormal (≥ 140 mg/dL)[7, 9]. Although both methods effectively detect GDM, they do so at different rates; however, research indicates no significant difference in maternal or neonatal complications between the two. Moreover, ACOG continues to endorse the two-step approach[7, 9-12]

Despite its effectiveness, the two-step approach primarily diagnoses GDM after 24–28 weeks of gestation and requires women to ingest glucose each time. Accordingly, both ACOG (2018) and the American Diabetes Association (ADA, 2023) suggest considering earlier screening (i.e., in the first trimester or at the first antenatal visit) for women at high risk of undiagnosed type 2 diabetes or early GDM—especially those with risk factors such as age over 35, obesity, a family history of diabetes, cardiovascular disease, or polycystic ovarian syndrome[9, 10]. Nevertheless, the optimal test for early screening remains undetermined[10].

Hemoglobin A1c (HbA1c) has drawn interest as a potential early screening tool because it reflects average blood glucose levels over the past 8–12 weeks[13]. It is widely used for diagnosing and monitoring nonpregnant patients with diabetes, generally applying an HbA1c ≥ 6.5% threshold to define diabetes[9, 14]. Furthermore, ADA (2023) guidelines advise HbA1c < 6.5% for women planning pregnancy to reduce congenital malformations, such as anencephaly, congenital heart disease, and renal anomalies, and to lower the risks of preeclampsia, fetal overgrowth, and preterm birth[10, 16–19]. During pregnancy, however, accelerated red blood cell turnover usually results in lower HbA1c levels than in nonpregnant individuals. Thus, ADA 2023 recommends an HbA1c target below 6.0% for most pregnant women, adjusting as needed to avoid maternal hypoglycemia[15].

Studies from multiple settings indicate that HbA1c might serve as an effective early screening test for GDM. One retrospective cohort study[20] showed that women with HbA1c values of 5.7–6.4% before 20 weeks were three times more likely to develop GDM than those with HbA1c < 5.7% (adjusted odds ratio 2.4). Another retrospective study[21] found that HbA1c ≤ 5.5% exhibited a negative predictive

value of 97%, demonstrating its capacity to rule out GDM early in pregnancy. Additional research comparing HbA1c with the 50g GCT[22] suggests that HbA1c has a lower threshold in pregnant women than in nonpregnant patients, making it a viable alternative for those unable to tolerate glucose ingestion. A prospective observational study[23] likewise supported HbA1c > 5.6% as a useful cutoff for detecting early GDM among high-risk pregnancies.

In summary, an internationally accepted strategy for early pregnancy GDM screening—particularly for high-risk women—has yet to be established. Emerging evidence nevertheless indicates that first-trimester HbA1c may reveal occult dysglycaemia well before the conventional 24-28 week window. On this premise, the present study measured HbA1c together with the 50 g GCT at the first antenatal visit in all high-risk pregnant women. Our primary objective was to determine the diagnostic accuracy of early pregnancy HbA1c as an adjunct to the conventional two-step screening strategy (50 g GCT followed by the 100 g OGTT reference test) and to quantify the incremental benefit that this combined approach offers for the early detection of gestational diabetes mellitus in Thai clinical practice.

Materials and Methods

This retrospective study was carried out at Bangkok Metropolitan Administration General Hospital (Klang hospital), to assess the accuracy of HbA1c for the early detection of GDM in women before 20 weeks of gestation. We reviewed the medical records of pregnant women who received antenatal care between 2023 and 2024. Participants were considered high-risk for GDM according to criteria adapted from both the Royal Thai College of Obstetricians and Gynecologists (RTCOG) and the ACOG Practice bulletin[10, 24]. The sample size was calculated based on the specificity of HbA1c at the 5.5% threshold (68%), as reported by Haddad et al[21], and an anticipated gestational diabetes mellitus (GDM) prevalence of 27.4% from institutional data. To estimate specificity with adequate precision (α = 0.05, d = 0.10), and accounting for a 20% attrition rate, a minimum of 139 participants was required.

Eligible individuals were 18–45 years of age, had a gestational age < 20 weeks, and fulfilled at least one high-risk criterion for GDM. These criteria included advanced maternal age (≥ 35 years), a first-degree relative with diabetes, a history of impaired glucose tolerance or HbA1c ≥ 5.7% before pregnancy, cardiovascular disease, or polycystic ovarian syndrome (PCOS). Obstetric risk factors encompassed previous GDM, a prior infant birth weight ≥ 4,000 g, unexplained stillbirth, recurrent pregnancy loss, and hydramnios. Physical-examination risk factors consisted of BMI ≥ 25 kg/m², hypertension (≥ 140/90 mmHg) coupled with BMI ≥ 23 kg/m², clinical signs of insulin resistance such as BMI ≥ 40 kg/m² or acanthosis nigricans, and glycosuria ≥ 1+ on at least two occasions[10, 24]. Women with preexisting diabetes, incomplete HbA1c or GDM screening data, or those who experienced fetal demise were excluded.

All included women underwent HbA1c testing at their first antenatal visit using the Cobas® Tina-quant Hemoglobin A1c Gen.3 assay, which is National Glycohemoglobin Standardization Program-certified and diabetes control and complications trial-standardized[25]. Based on established thresholds, HbA1c was categorized as < 5.7% (low risk), 5.7–6.4% (intermediate risk), or ≥ 6.5% (diabetes)[9, 14, 15]. Each participant also received the 50g GCT without fasting; a 1-hour blood glucose ≥ 140 mg/dL was considered abnormal[10]. Any woman with an abnormal 50g GCT underwent a 100g OGTT, interpreted using the Carpenter-Coustan criteria[12, 26].

Women with an HbA1c ≥ 6.5 % were classified as having overt diabetes mellitus and referred to an endocrinologist for definitive management. The diagnostic performance of early pregnancy HbA1c and the 50 g GCT was assessed against the 100 g OGTT, which served as the reference ("gold-standard") for GDM diagnosis. Women whose HbA1c fell between 5.7 % and 6.4 % or who produced an abnormal 50 g GCT result underwent a confirmatory 100 g OGTT. Participants with HbA1c < 5.7 % and a

normal 50 g GCT were re-screened at 24–28 weeks in accordance with the standard two-step ACOG protocol[9, 10]. A simplified outline of this screening strategy is shown in Fig. 1.

Data was analyzed using STATA 17.0. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were presented as frequencies (%). For comparisons, unpaired t-tests were used for continuous data, and chi-square or Fisher's exact tests were employed for categorical data. A p value < 0.05 was regarded as statistically significant. To identify the optimal HbA1c cutoff, we constructed a receiver operating characteristic (ROC) curve and computed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The performance of HbA1c was compared to that of the 50g GCT, which is widely used in clinical practice but is not definitively considered a gold standard for early GDM screening[10, 23].

This study was approved by the Bangkok Metropolitan Administration Human Research Ethics Committee (BMAHREC). Because this research involved only the retrospective review of medical records, participants faced no additional risks, and all patient data were anonymized. Women diagnosed with GDM were managed according to institutional prenatal care guidelines, including self-monitoring of blood glucose, dietary counseling, and referral to specialists as needed.

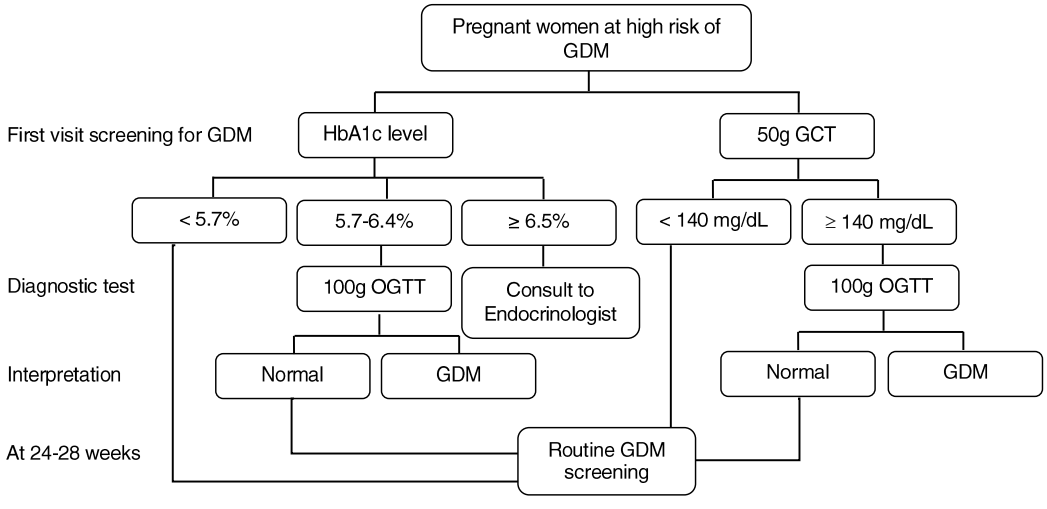

Fig. 1. Screening and diagnostic pathway for gestational diabetes mellitus (GDM) in high-risk pregnant women.

GDM: gestational diabetes mellitu, HbA1c: hemoglobin A1c, GCT: glucose challenge test, OGTT: oral glucose tolerance test

Results

A total of 463 pregnant women attended antenatal care (ANC) at Bangkok Metropolitan Administration General Hospital between January 2023 and April 2024. Following the inclusion criteria, 379 participants met the eligibility requirements for this study. A total of 97 women were excluded due to pre-existing diabetes (n = 21), lack of glucose screening (n = 4), fetal demise (n = 14), severe fetal anomalies leading to pregnancy termination (n = 2), molar pregnancy (n = 1), chromosomal abnormalities (n = 1), or incomplete data due to ANC transfer to other facilities (n = 54). This left 282 participants for final analysis (Fig. 2).

The baseline characteristics of the study population are summarized in Table 1. The mean maternal age was 30.71 ± 5.88 years, and the mean pre-pregnancy BMI was 25.69 ± 5.04 kg/m², with

55.3% (n = 156) classified as overweight or obese (BMI ≥ 25 kg/m²). Among the participants, 31.6% (n = 89) were primigravida, while 68.4% (n = 193) had previous pregnancies. The history of GDM in previous pregnancies was noted in 6.7% (n = 19) of cases. The mean HbA1c level was 5.19 ± 0.43%, and 45.4% (n = 128) had a positive 50g GCT (≥ 140 mg/dL). The overall GDM diagnosis rate was 29.8% (n = 84), with 20.2% (n = 57) diagnosed before 20 weeks of gestation and 9.6% (n = 27) diagnosed after 20 weeks. A small proportion, 3.2% (n = 9), required insulin therapy.

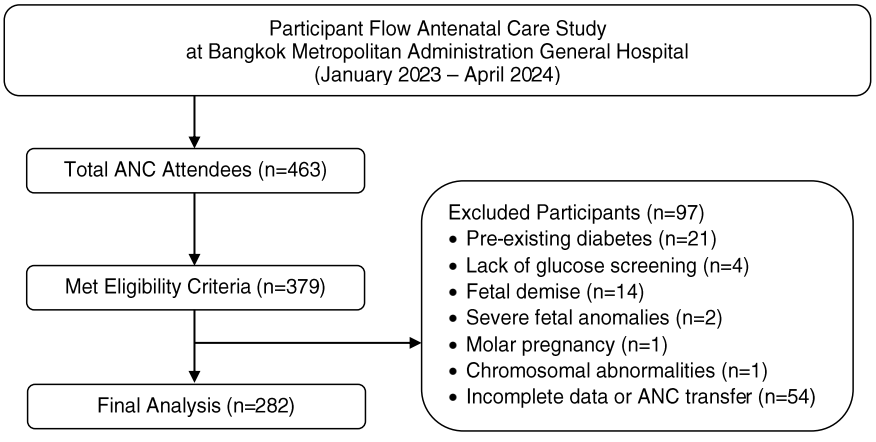

Fig. 2. Flowchart of participant selection for the study.

Table 1. Demographics of study population.

Demographics of study population	
Variable	**n = 282**
Age (years), mean ± SD	30.71 ± 5.88
Pre-pregnancy BMI (kg/m²), mean ± SD	25.69 ± 5.04
BMI ≥ 25 (kg/m²), n (%)	156 (55.3%)
Parity	
- Nulliparous, n (%)	89 (31.6%)
- Multiparous, n (%)	193 (68.4%)
Previous pregnancy GDM, n (%)	19 (6.7%)
HbA1c value (%), mean ± SD	5.19 ± 0.43
50 g GCT ≥ 140 mg/dL (screening test positive), n (%)	128 (45.4%)
GA at screening test	11 weeks 1 day
GDM diagnosis during pregnancy, n (%)	84 (29.8%)
Diagnosis GDM at GA ≤ 20 weeks, n (%)	57 (20.2%)
Diagnosis GDM at GA > 20 weeks, n (%)	27 (9.6%)
Need insulin treatment, n (%)	9 (3.2%)

BMI: body mass index, GDM: gestational diabetes mellitus, GCT: glucose challenge test, GA: gestational age, SD: standard deviation

Among the 282 participants, 38 women (13.5%) had HbA1c levels between 5.7–6.4%, while 244 women (86.5%) had HbA1c < 5.7%. The comparative analysis revealed significant differences in metabolic

parameters (Table 2).

Women in the HbA1c 5.7–6.4% group had significantly higher pre-pregnancy BMI ($p < 0.001$) and were more likely to have BMI ≥ 25 kg/m² ($p = 0.005$). The GDM diagnosis rate was significantly higher in this group (71.1% vs 23.4%, $p < 0.001$), with more cases diagnosed before 20 weeks ($p < 0.001$). The need for insulin therapy was also significantly increased ($p < 0.001$).

To assess whether HbA1c 5.7–6.4% could be a substitute for 50g GCT, a direct comparison was conducted between HbA1c 5.7–6.4% (n = 38) and GCT ≥ 140 mg/dL (n = 128), with key findings summarized in Table 3.

Table 2. Outcome based on screening test results between HbA1c < 5.7% and HbA1c 5.7 - 6.4%.

Outcome based on screening test results between HbA1c < 5.7% and HbA1c 5.7 - 6.4%			
Variable	**HbA1c < 5.7% (n = 244)**	**HbA1c 5.7 - 6.4% (n = 38)**	**p value**
Age (years), mean ± SD	30.62 ± 5.94	31.29 ± 5.51	0.516
Advanced maternal age (≥ 35-year-old)	73 (29.9%)	11 (28.9%)	0.903
Pre-pregnancy BMI (kg/m²), mean ± SD	25.27 ± 4.95	28.44 ± 4.82	< 0.001*
BMI ≥ 25 (kg/m²), n (%)	127 (52%)	29 (76.3%)	0.005*
Parity			0.261
- Nulliparous, n (%)	80 (32.8%)	9 (23.7%)	
- Multiparous, n (%)	164 (67.2%)	29 (76.3%)	
Previous pregnancy GDM, n (%)	15 (6.1%)	4 (10.5%)	0.317
GDM diagnosis during pregnancy, n (%)	57 (23.4%)	27 (71.1%)	< 0.001*
Diagnosis GDM at GA ≤ 20 weeks, n (%)	35 (14.3%)	22 (57.9%)	< 0.001*
Diagnosis GDM at GA > 20 weeks, n (%)	22 (9%)	5 (13.2%)	0.42
Need insulin treatment, n (%)	4 (1.6%)	5 (13.2%)	< 0.001*

SD: standard deviation, BMI: body mass index, GDM: gestational diabetes mellitus, GA: gestational age

Table 3. Baseline characteristics and pregnancy outcomes in participants with HbA1c 5.7–6.4% versus 50-g glucose challenge test (GCT ≥ 140 mg/dL).

Variable	HbA1c 5.7–6.4% (n = 38)	GCT ≥ 140 mg/dl (n = 128)	p value
Age (years), mean ± SD	31.29 ± 5.51	31.72 ± 5.65	0.68
Advanced maternal age (≥ 35-year-old), n (%)	11 (28.9%)	45 (35.2%)	0.477
Pre-pregnancy BMI (kg/m²), mean ± SD	28.44 ± 4.82	26.08 ± 4.85	0.009*
BMI ≥ 25 (kg/m²), n (%)	29 (76.3%)	71 (55.5%)	0.021*
Parity			0.325
- Nulliparous, n (%)	9 (23.7%)	41 (32%)	
- Multiparous, n (%)	29 (76.3%)	87 (68%)	
Previous pregnancy GDM, n (%)	4 (10.5%)	8 (6.3%)	0.371
GDM diagnosis during pregnancy, n (%)	27 (71.1%)	72 (56.3%)	0.102
Diagnosis GDM at GA ≤ 20 weeks, n (%)	22 (57.9%)	55 (43%)	0.105
Diagnosis GDM at GA > 20 weeks, n (%)	5 (13.2%)	17 (13.3%)	0.984
Need insulin treatment, n (%)	5 (13.2%)	9 (7%)	< 0.001*

SD: standard deviation, BMI: body mass index, GDM: gestational diabetes mellitus, GA: gestational age

The results indicated that women in the HbA1c 5.7–6.4% group had significantly higher pre-pregnancy BMI and were more likely to require insulin therapy compared to the GCT ≥ 140 mg/dL group ($p < 0.001$). However, the overall GDM diagnosis rate was not significantly different between the two groups ($p = 0.102$).

The ROC curve analysis was conducted to assess the diagnostic performance of HbA1c for early GDM detection, yielding an area under the curve (AUC) of 0.716 (95%CI 0.635–0.798), indicating acceptable diagnostic accuracy. Since an AUC between 0.7–0.8 suggests acceptable diagnostic accuracy, this supports the feasibility of HbA1c as a screening tool (Fig. 3).

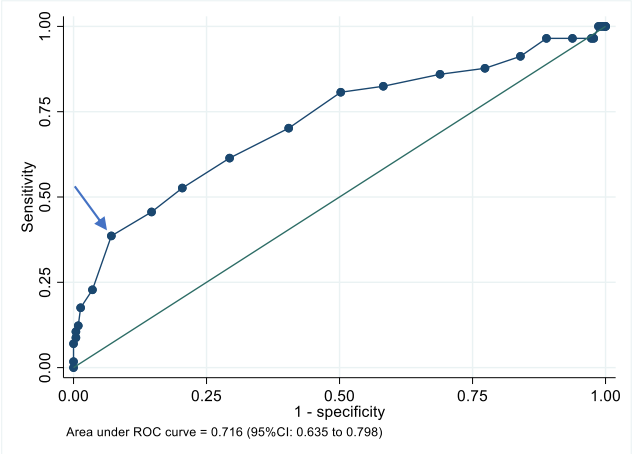

Fig. 3. Receiver operating characteristic curve for HbA1c cutoff in early GDM screening.

Further analysis using the Youden Index initially suggested that an HbA1c cutoff of ≥ 5.5% provided an optimal balance of sensitivity (52.6%), specificity (79.6%), and overall accuracy (74.1%). However, we selected ≥ 5.7% due to its notably higher specificity (92.9%), resulting in fewer false positives. Although this cutoff yields a lower sensitivity (38.6%)—and might therefore miss some early GDM cases—it remains effective for confirming high-risk pregnancies and reducing overdiagnosis. Meanwhile, HbA1c ≥ 6.0% demonstrated near-perfect specificity (99.1%) but very low sensitivity (12.3%), limiting its practicality for broad screening while underscoring its potential to identify severe cases.

Consequently, using HbA1c 5.7–6.4% as a threshold is a practical approach for pinpointing women who should undergo further evaluation

with the 50-g glucose challenge test (50g GCT) and, if indicated, confirmatory testing via the 100-g oral glucose tolerance test (OGTT) (Table 4).

Table 4. Receiver operating characteristic analysis for determining the optimal HbA1c cutoff in early gestational diabetes detection.

HbA1C cutoff ≥	True +	False +	False -	True -	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy	False positive rate (%)
3.6	57	224	0	1	100.0%	0.4%	20.3%	100.0%	20.6%	99.6%
3.8	57	223	0	2	100.0%	0.9%	20.4%	100.0%	20.9%	99.1%
4.1	57	222	0	3	100.0%	1.3%	20.4%	100.0%	21.3%	98.7%
4.4	55	220	2	5	96.5%	2.2%	20.0%	71.4%	21.3%	97.8%
4.5	55	219	2	6	96.5%	2.7%	20.1%	75.0%	21.6%	97.3%
4.6	55	211	2	14	96.5%	6.2%	20.7%	87.5%	24.5%	93.8%
4.7	55	200	2	25	96.5%	11.1%	21.6%	92.6%	28.4%	88.9%
4.8	52	189	5	36	91.2%	16.0%	21.6%	87.8%	31.2%	84.0%
4.9	50	174	7	51	87.7%	22.7%	22.3%	87.9%	35.8%	77.3%
5.0	49	155	8	70	86.0%	31.1%	24.0%	89.7%	42.2%	68.9%
5.1	47	131	10	94	82.5%	41.8%	26.4%	90.4%	50.0%	58.2%
5.2	46	113	11	112	80.7%	49.8%	28.9%	91.1%	56.0%	50.2%
5.3	40	91	17	134	70.2%	59.6%	30.5%	88.7%	61.7%	40.4%
5.4	35	66	22	159	61.4%	70.7%	34.7%	87.8%	68.8%	29.3%
5.5	30	46	27	179	52.6%	79.6%	39.5%	86.9%	74.1%	20.4%
5.6	26	33	31	192	45.6%	85.3%	44.1%	86.1%	77.3%	14.7%
5.7	22	16	35	209	38.6%	92.9%	57.9%	85.7%	81.9%	7.1%
5.8	13	8	44	217	22.8%	96.4%	61.9%	83.1%	81.6%	3.6%
5.9	10	3	47	222	17.5%	98.7%	76.9%	82.5%	82.3%	1.3%
6.0	7	2	50	223	12.3%	99.1%	77.8%	81.7%	81.6%	0.9%
6.1	6	1	51	224	10.5%	99.6%	85.7%	81.5%	81.6%	0.4%
6.2	5	1	52	224	8.8%	99.6%	83.3%	81.2%	81.2%	0.4%
6.3	4	0	53	225	7.0%	100.0%	100.0%	80.9%	81.2%	0.0%
6.4	1	0	56	225	1.8%	100.0%	100.0%	80.1%	80.1%	0.0%

PPV: positive predictive value, NPV: negative predictive value

The predictive capability of HbA1c 5.7–6.4% in estimating the likelihood of 50g GCT positivity (≥ 140 mg/dL) was analyzed, with the results presented in (Table 5).

Table 5. Predictive value of HbA1c 5.7–6.4% for 50g GCT (≥ 140 mg/dL) positivity.

Screening method	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Accuracy (%) (95%CI)
HbA1c 5.7-6.4%	23.44 (16.41 - 31.74)	94.81 (90.02 - 97.73)	78.95 (62.68 - 90.45)	59.84 (53.39 - 66.04)	62.4 (56.5 – 68.1)

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

Among individuals with HbA1c 5.7–6.4%, the probability of obtaining a positive 50g GCT result was reflected in the positive predictive value (PPV) of 78.9%, indicating that nearly four out of five women with HbA1c 5.7–6.4% were likely to have a GCT ≥ 140 mg/dL. Conversely, the negative predictive value (NPV) was 59.8%, suggesting that among those with HbA1c < 5.7%, approximately six out of ten women would have a GCT result below the threshold of 140 mg/dL.

The overall sensitivity of 23.4% implies that HbA1c 5.7–6.4% captures only a small proportion of those who will test positive on the 50g GCT, while the specificity of 94.8% demonstrates that those with HbA1c below 5.7% are highly unlikely to have GCT ≥140 mg/dL. The accuracy of 62.4% indicates moderate predictive reliability of HbA1c in estimating 50g GCT positivity.

These findings suggested that while HbA1c 5.7–6.4% strongly predicted a positive 50g GCT (high PPV), its low sensitivity limited its ability to detect all potential positive cases. This statistical insight can aid in understanding the role of HbA1c as a potential risk stratification marker for GDM screening.

Table 6 shows that an HbA1c threshold of 5.7–6.4% yields an overall diagnostic accuracy of 81.9% (95 %CI 76.9–86.2) to predict early GDM, surpassing the 73.4% (95 %CI 67.8–78.5) achieved with the conventional 50 g GCT. This 8.5 percentage point advantage was driven by the markedly higher specificity of HbA1c (92.9% vs 67.6%), which offset its lower sensitivity (38.6 % vs 96.5 %). Consequently, a positive HbA1c more reliably indicated true GDM (PPV 57.9% vs 42.9%), whereas a negative 50 g GCT remained superior for ruling out the condition (NPV 98.7%).

Table 6. Diagnostic performance of HbA1c 5.7–6.4% and the 50g GCT in early detection of gestational diabetes mellitus.

Screening method	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Accuracy (%) (95%CI)
HbA1c 5.7 - 6.4%	38.6 (26 - 52.43)	92.89 (88.71 - 95.88)	57.89 (40.82 - 73.69)	85.66 (80.62 - 89.8)	81.91 (76.92 – 86.23)
50g GCT ≥ 140 mg/dL	96.49 (87.89 - 99.57)	67.56 (61.01 - 73.63)	42.97 (34.26 - 52.01)	98.7 (95.39 - 99.84)	73.4 (67.84 – 78.47)

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

Discussion

This retrospective analysis of 282 high-risk Thai pregnant women revealed a significant burden of dysglycemia, with 29.8% diagnosed with gestational diabetes mellitus (GDM) and 20.2% identified by or before 20 weeks of gestation. These rates were higher

than the 14.4% early-GDM prevalence reported in a population-based first-trimester cross-sectional Thai study[27] and exceed the 16.4% total GDM prevalence found in the large prospective study[28]. This elevated prevalence was primarily attributable to the intentional recruitment of high-risk women (mean pre-pregnancy BMI 25.7 kg/m²; 55% overweight or obese) and systematic early screening with both HbA1c and the 50 g GCT at a median gestational age of 11 weeks. Early testing may have captured previously high risk for GDM, consistent with findings from Hinkle et al, who observed that 0.1% increase in first-trimester HbA1c was associated with a 22% increased risk of GDM[29].

Comparative data from Thai studies demonstrated a clear trend: elevated BMI was associated with a higher incidence of early GDM. Our study population's average BMI 25.7 kg/m² lied between the lean cohort (mean BMI 24.4 kg/m²)[30] and the heavier group[31], in which 78% had a BMI > 22.9 kg/m². This aligned with international findings suggesting that a first-trimester HbA1c ≥ 5.7% may reflect underlying beta-cell dysfunction even before full insulin resistance develops[32], highlighting the need for population-adapted screening thresholds.

The predictive performance of HbA1c at a threshold of 5.7% in our study demonstrated a specificity of 92.9%, sensitivity of 38.6%, and an area under the curve (AUC) of 0.716, indicating acceptable discriminative ability. This compares favourably with previously reported thresholds, such as 5.4% (AUC 0.706, sensitivity 61.8%, specificity 68.3%)[33], 5.45% (AUC 0.84, sensitivity 54.8%, specificity 96.8%)[28], and 5.8% (specificity 100%, sensitivity 17.1%)[30], although the latter studies involved participants screened beyond 24 weeks' gestation. In contrast, the 50 g GCT at a threshold of ≥ 140 mg/dL yielded a sensitivity of 96.5%, specificity of 67.6%, PPV of 43.0%, NPV of 98.7%, and overall accuracy of 73.4%. HbA1c testing, by comparison, offered higher specificity and superior overall accuracy (81.9%). These findings illustrated the trade-off between maximizing case detection and minimizing false positives and support the role of HbA1c at 5.7% as an efficient and practical early adjunct to conventional GDM screening. This approach may be particularly advantageous in resource-limited settings or for pregnant women unable to tolerate oral glucose ingestion.

A unique strength of our study was the generation of a detailed ROC matrix encompassing HbA1c values from 3.6% to 6.4% increments in 0.1%. This provided a flexible framework for customizing screening thresholds based on institutional prevalence rates and local resource availability. For example, high-risk maternal-fetal clinics aiming to minimize false negatives may adopt a threshold of 5.4% (sensitivity ≈ 60%, likelihood ratio (LR) 0.59), consistent with data[33], facilitating timely referral for OGTT. Conversely, community hospitals facing OGTT overcapacity may choose a threshold of 5.7% to achieve specificity > 90% (LR+ ≈ 5.4), as reported[28, 32], where HbA1c ≥ 5.7% effectively predicted insulin requirement (odds ratio ≈ 4) and correlated with a 2- to 4-fold increased risk of delivering large for gestational age neonates.

Strengths of this study included its real-world, resource-conscious design, targeted focus on high-risk Asian populations, and early gestational data collection. Limitations comprised its retrospective single-center nature, modest sample size, and the potential for ethnic bias in HbA1c interpretation. Additionally, which limited the generalizability of specificity and overall accuracy estimates. Nonetheless, post hoc 95%CI for specificity (88.7–95.9%) and accuracy (76.9–86.2%) supported the internal validity of our findings. Future prospective studies in broader-risk populations with larger sample sizes are warranted to refine the HbA1c cutoff and validate these performance indices.

Conclusion

In conclusion, HbA1c measured before 20 weeks in the 5.7–6.4% range cannot replace glucose-based testing due to its limited sensitivity. However, with high specificity and an overall accuracy of 81.9%, it served as a valuable adjunct to the 50 g GCT within

the two-step screening protocol. First-trimester HbA1c enhances diagnostic precision, facilitates early risk stratification, and offers a pragmatic alternative when glucose loading is intolerant (e.g., severe hyperemesis gravidarum), thereby improving both clinical efficiency and the quality of GDM detection in high-risk Thai pregnancies.

Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Anomalies Detected in Third Trimester – A prospective descriptive study

Noorjahan Thirunilath, MBBS, MS (OBG)*,
Smitha D'Couth, MBBS, DGO, MS (OBG)*

** Department of Obstetrics & Gynaecology, Govt. Medical College, Kozhikode, Kerala, India*

ABSTRACT

Objectives: To detect the incidence of structural anomalies diagnosed by third trimester ultrasound after a normal anomaly scan and classify them according to major organ systems and types.

Materials and Methods: It was a prospective descriptive study of antenatal women who had a negative second trimester anomaly screening with a newly detected fetal anomaly in the routine third trimester ultrasound conducted in the Department of Obstetrics and Gynaecology of Government Medical College, Kozhikode over a period of 18 months from September 2020 to February 2022. These women were followed-up till delivery and neonatal outcomes were measured.

Results: The incidence of congenital anomalies detected in third trimester was 0.7% (110 cases in 15,560 deliveries). Majority of them were of urogenital system (32.7%) followed by cardiovascular system (21.8%). Commonest anomaly detected was hydronephrosis, followed by congenital diaphragmatic hernia, ventricular septal defect, ventriculomegaly and corpus callosal agenesis.

Conclusion: The ultrasound examination of third trimester is of additional benefit and can detect previously undiagnosed fetal anomalies especially development dependant anomaly like agenesis of corpus callosum and progressing anomalies like gastrointestinal and skeletal anomaly. This can help in subsequent management including counselling of parents, planning of place, time, mode of delivery and also to plan neonatal interventions.

Keywords: fetal structural abnormalities, third trimester ultrasound, neonatal morbidity.

Correspondence to: *Smitha D'Couth, MBBS, DGO, MS (OBG), Department of Obstetrics & Gynaecology, Govt. Medical College, Kozhikode. E-mail: smithasebin@gmail.com*

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Introduction

Major congenital anomalies occur in 3 to 4% and minor anomalies occur in 7% to 10% of the population. Anomalies are associated with increased risk of aneuploidy, genetic syndromes, and poor neonatal outcome[1]. Ultrasound scan is the primary imaging modality for the detection of congenital anomalies. Ultrasound scan at 11 – 14 weeks of gestation not only assess the risk of chromosomal abnormalities by measuring nuchal translucency but also detect major fetal malformations at this gestational age. The targeted anomaly scan is performed between 18 – 23 weeks. The overall detection rate for structural anomalies with nuchal translucency (NT) scan and second trimester ultrasound is approximately 68%. Third-trimester ultrasound scan is mainly used to assess fetal growth, amniotic fluid index and fetal wellbeing. Rarely previously undetected or late evolving fetal anomalies are incidentally detected in third trimester ultrasound. Anomalies like small ventricular septal defect may remain undiagnosed in the first-and second-trimester scans[2]. Malformations of central nervous system like agenesis of corpus callosum, gastrointestinal anomalies like bowel obstruction and atresia, some nonlethal skeletal dysplasias will develop and get manifested during the late second or third trimester[3]. Our institutional protocol includes routine ultrasonogram for all pregnant women in the last trimester to assess fetal growth, preferably between 32 – 34 weeks and even earlier, or serially if growth restriction is suspected. The objective of this study was to find out the incidence of congenital malformations detected by third trimester ultrasound scan in antenatal women with normal first and second trimester scans and to identify the major organ systems affected by late evolving anomalies. It was also aimed to find out the neonatal morbidity in the study population.

Materials and Methods

This was a prospective descriptive study conducted in the Department of Obstetrics and Gynaecology and Neonatal unit in the Institute of Maternal and Child Health of Government Medical College Kozhikode in Kerala, India from September 2020 to February 2022 after getting Institutional Ethics Committee approval. Antenatal women with singleton pregnancies, having normal NT and targeted anomaly scans, with newly detected fetal anomalies in ultrasonogram performed after 28 weeks for fetal growth assessment, were included in this study. Informed consent was obtained before recruiting each woman into the study. Antenatal women with positive aneuploidy screening, fetal anomalies detected in NT or second trimester scan and multiple pregnancy were excluded.

Antenatal women satisfying the inclusion criteria were identified. The type of anomaly detected was recorded. Detailed history was taken using a proforma which included obstetric score, maternal complications, past obstetric history, family history of anomalies, intake of any drugs during pregnancy or any maternal infection. They were followed-up till delivery and the findings were confirmed postnatally. Fetal outcomes were measured in terms of neonatal intensive care unit (NICU) admission, neonatal morbidity, intrauterine demise (IUD), neonatal death (NND) and any surgery/ intervention in the newborn period. Data was entered in Microsoft Excel worksheet and was analysed using appropriate statistical method.

Results

Total number of births during the study period was 15,560 and total number of congenital anomalies detected by antenatal ultrasonogram were 353 (2.26%). 110 fetal anomalies were detected after 28 weeks of gestation with an incidence of 0.7% of the total births. This accounted to 31.16% of the total anomalies.

Table 1 shows system wise distribution of anomalies detected by third trimester scan. Renal and urogenital anomalies were the commonest (32.7%) followed by cardiovascular anomalies (21.8%).

Table 1. System wise distribution of anomalies.

System	Number	Percentage	Gestational age at diagnosis (in weeks)	
			Mean	Range
Central nervous system	18	16.3	34	28 -38
Cardiovascular system	24	21.8	33.4	30 -37
Renal and Genito-urinary system	36	32.7	34.5	29 -38
Gastrointestinal system	9	8.1	34.2	31 -37
Thoracic anomalies	12	10.9	33.2	30 -36
Skeletal system	8	7.2	32.3	29 -36
Others	3	2.7	32.6	31 -34
Total	**110**			

The different central nervous system (CNS) anomalies detected in the third trimester are shown in Table 2. CNS anomalies constituted 16.3% of anomalies detected by third trimester ultrasound, of which ventriculomegaly and dysgenesis of corpus callosum were the most common. The median gestational age of detection of CNS anomalies was 34 weeks (range 28–38). Follow-up was advised in majority of the babies after postnatal magnetic resonance imaging (MRI) confirmation of sonographic findings. Babies with fetal microcephaly underwent karyotyping and was normal. Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus (TORCH) screening was also negative in them. Mother of one baby with microcephaly was positive for cytomegalovirus immunoglobulin M (IgM) antibodies. Mother was toxoplasma IgM positive in neonate with bilateral ventriculomegaly with intra parenchymal haemorrhage. The baby with gross hydrocephalus had neonatal death.

Table 2. Central nervous system anomalies.

Central nervous system anomalies	Number
Mild ventriculomegaly	3
Moderate ventriculomegaly	1
Arachnoid cyst	1
Blakes pouch cyst	1
Hydrocephalus	2
Absence or dysgenesis of corpus callosum	4
Cerebellar hypoplasia	1
Microcephaly	3
Schizencephaly	1
Bilateral ventriculomegaly with intra parenchymal hemorrhage	1
Total	**18**

24 cardiovascular anomalies were detected in the third trimester (21.8%) as seen in Table 3, out of which ventricular septal defect (VSD) (4 cases) was the most common anomaly. Two babies who had transposition of great arteries (TGA) with VSD were advised corrective surgery after 6 weeks. The 3 babies with tetralogy of Fallot (TOF) were advised corrective surgery later as there was no cyanotic spell or saturation fall in the neonatal period.

Table 3. Cardiovascular system anomalies.

Cardiovascular system anomalies	Number
Ventricular septal defect	4
Tetralogy of Fallot	3
Cardiogenic hydrops	1
Hypoplastic right heart syndrome with pulmonary valve atresia	1
Fetal cardiomegaly	1
Fetal pericardial effusion	2
Transposition of great arteries (TGA) with ventricular septal defect	2
Transposition of great arteries	1
Ebstein anomaly	1
Coronary sinus atrial septal defect	1
Double outlet right ventricle	1
Right sided aortic arch dilatation	2
Cardiac rhabdomyoma	2
Hypoplastic left heart syndrome (HLHS)	1
Hypoplastic pulmonary artery	1
Total	**24**

Antenatal sonographic finding of Ebstein anomaly was dilated right atrium with mild tricuspid regurgitation; postnatal echo showed very small atrialised right ventricle with patent ductus arteriosus (PDA) and dilated right atrium. Baby was managed postnatally with prostaglandin infusion and was advised tricuspid valve corrective surgery later. Baby with double outlet right ventricle (DORV) had severe pulmonary artery hypertension in the neonatal period and was planned for pulmonary artery banding at 6 weeks. The baby with hypoplastic right heart syndrome with pulmonary valve atresia was referred to higher cardiology centre immediately after birth and underwent Blalock-Taussig shunt on 4th postnatal day.

Neonatal death occurred in babies with TGA, hypoplastic left heart syndrome and cardiogenic hydrops. TGA baby also had anal atresia which was diagnosed postnatally. Other babies were kept under follow-up.

Gastrointestinal anomalies as seen in Table 4 constituted only 8.1% of the third trimester anomalies of which commonest was duodenal atresia (n = 3). One baby with duodenal atresia was detected to have trisomy 21 on postnatal evaluation. Two babies with duodenal atresia underwent open duodeno-duodenostomy. One antenatally detected case of duodenal atresia was diagnosed as gut malrotation in the postnatal period and baby underwent Ladds procedure.

Table 4. Gastrointestinal system anomalies.

Gastrointestinal system anomalies	Number
Esophageal atresia	1
Duodenal atresia	3
Jejunal atresia	1
Choledochal cyst	2
Cystic biliary atresia	1
Fetal intestinal obstruction	1
Total	**9**

The baby with esophageal atresia, detected in the early third trimester due to absence of stomach bubble and polyhydramnios expired on third postnatal day. In the fetus with jejunal atresia, antenatal ultrasound showed polyhydramnios with dilated stomach and upper gastrointestinal tract. Baby developed abdominal distension and bilious vomiting in the postnatal period and underwent emergency exploratory laparotomy with jejunal resection, but expired postoperatively.

One antenatally detected choledochal cyst was a transient finding which was not seen in the postnatal period. Other case of choledochal cyst was confirmed postnatally and was advised Roux-en-y choledocho-jejunostomy after 6 weeks. Baby with intestinal obstruction underwent exploratory laparotomy, resection and ileo-colic anastomosis and the cause for obstruction was meconium ileus. Kasai procedure was advised after one month in the baby with cystic biliary atresia.

Urogenital system was the most affected system (36 cases) of which 24 were varying degrees of hydronephrosis as shown in Table 5. All newborns with antenatal hydronephrosis underwent postnatal evaluation and Ultrasound of the Kidneys, Ureters & Bladder (KUB). Babies with posterior urethral valve underwent cystoscopy and posterior urethral valve (PUV) fulguration. 8 cases of mild hydronephrosis were a transient finding which was not seen postnatally.

Table 5. Urogenital anomalies.

Urogenital Anomalies	Number
Fetal ectopic kidney	2
Distended fetal urinary bladder	2
Mild hydronephrosis (renal pelvis dilatation 7-9 mm)	15
Moderate hydroureteronephrosis (renal pelvis dilatation 10 -15 mm)	3
Gross hydroureteronephrosis (renal pelvis dilatation > 15 mm) with posterior urethral valve	6
Polycystic kidney disease	1
Single umbilical artery, bilateral gross renal hydronephrosis.	1
Fetal congenital mega ureter	2
Ovarian cyst	1
Fetal bilateral hydrocoele	1
Duplex kidney	2
Total	**36**

Some babies with hydroureteronephrosis (HUN) had VUR (vesicoureteric reflex) and were given prophylactic antibiotics and strict follow-up was advised. Other anomalies like anal atresia, ambiguous genitalia and para-ureteric diverticulum and coarctation of aorta were detected postnatally in the baby with gross HUN and single umbilical artery.

There were 8 skeletal system anomalies of which 4 were congenital talipes equinovarus (CTEV), 3 were achondroplasia and one Binders syndrome with nonlethal skeletal dysplasia. Babies with CTEV were advised serial casting as per Ponsetti technique. All other cases were advised follow-up.

Of the thoracic anomalies detected in the third trimester, congenital diaphragmatic hernia (CDH) was the commonest as shown in Table 6. Five babies with CDH underwent surgical repair of which one expired postoperatively. Other three babies expired before surgery, two due to severe persistent pulmonary hypertension and one due to pneumothorax with metabolic acidosis.

Table 6. Thoracic anomalies.

Thoracic anomalies	Number
Congenital diaphragmatic hernia	8
Congenital pulmonary airway malformation (CPAM)	2
Pulmonary hypoplasia	1
Eventration of left diaphragm	1
Total	**12**

Baby with eventration of left diaphragm underwent left subcostal incision laparotomy plus plication. Both babies with congenital pulmonary airway malformation (CPAM) had type 1 malformation and had no evidence of hydrops or lung hypoplasia and were advised follow-up. A case of pulmonary hypoplasia with severe oligohydramnios was detected at 29 weeks while ultrasound evaluation of antepartum hemorrhage (APH). This fetus had intrauterine demise at 30 weeks.

Other anomalies detected in third trimester were one case each of cleft lip, sacrococcygeal teratoma and fetal neuroblastoma. Baby with sacrococcygeal teratoma had only sacral pit with deficient levator ani muscle and rectal herniation and corrective surgery was advised.

Majority (73.6%) of the fetal anomalies were detected in women between 20 to 30 years of age. There was only one mother above 40 years of age with USG showing gross HUN with single umbilical artery. 35.4 % of study population were primigravida and 64.5% were multigravida. 24.5% of the mothers (n = 27) had history of previous abortion and 3.6% (n = 4) had previous still birth or neonatal deaths. Three mothers had previous anomalous babies. Baby with hypoplastic right heart syndrome was the third child of that mother whose second child also had congenital heart disease (VSD)[11]. mothers had family history of anomalous babies.

Maternal complications in the study population are as seen in Table 7. Out of the total 110 cases 30.8% were diabetic. One patient each had toxoplasmosis and cytomegalovirus infection antenatally. Two mothers were taking teratogenic drugs like warfarin; sodium valproate and the anomalies were Binder's facies and mild ventriculomegaly respectively. Polyhydramnios was present in 13.6 %, oligohydramnios in 14.5% and normal amniotic fluid volume in 71.8% of cases.

Table 7. Maternal complications.

Maternal complications	Number	Percentage
Overt diabetes mellitus	5	4.5
Gestational diabetes mellitus	29	26.3
Congenital heart disease	2	1.8
Teratogenic drug intake	3	2.7
Maternal TORCH infection	2	1.8
Hypothyroidism	24	21.8
Uncomplicated	45	40.9

TORCH: Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus

Of the total cases, 70.9% anomalous babies were delivered vaginally and 29.09% by cesarean section (CS). Most of the CS were done for obstetric indications. The mean gestational

age at the time of delivery was 37.4 weeks with standard deviation (SD) of 2.59.

64 were male (58.2%) and 45 were female (40.9%). One baby was born with ambiguous genitalia. 73 babies had low birth weight (66.3%), of which 20.9% were very low birth weight babies. Mean birth weight was 2.2 kg (SD 0.77). Mean Apgar score at 1 minute and 5 minutes were 7.63 (SD 1.59) and 8.66 (SD 1.24) respectively. 61.8 % of babies needed NICU admission for further evaluation and management. 20% babies required surgical intervention in the neonatal period and 10% babies were advised surgical correction later. 9% babies became NND. Table 8 shows the procedures and interventions done postnatally.

Table 8. Neonatal procedure /intervention.

System	Total number	Anomaly corrected with surgery	Procedure	Observation/ follow-up	NND/IUD	Surgical correction later
CNS	18	nil	nil	17	1	nil
CVS	24	Right hypoplastic heart syndrome	Blalock Taussing shunt	20	3	a) TGA with VSD (2 cases) b) TOF (3 cases) c) Ebstein anomaly d) DORV
GIT	9	a) Duodenal atresia (2 cases)	open duodeno-duodenostomy	3	2	a) Choledochal cyst (6 weeks) b) Biliary atresia
		b) Gut malrotation	Ladds procedure			
		c) Jejunal atresia	Laparotomy with jejunal resection			
		d) Intestinal obstruction	Laparotomy with bowel resection and anastomosis			
Thoracic anomaly	12	CDH (5 cases)	Laparotomy and CDH repair	2	5	nil
		Left eventration of diaphragm	Left subcostal incision laparotomy plus plication			
Skeletal	8	nil	CTEV managed with serial casting	8		
Renal and genitourinary	36	Posterior urethral valve (6 cases)	Cystoscopy with PUV fulguration	30		
Others	3	Nil	nil	3	nil	a) Sacrococcygeal teratoma b) Cleft lip

NND: neonatal death, IUD: intrauterine demise, CNS: central nervous system, CVS: chorionic villus sampling, TGA: transposition of great arteries, VSD: ventricular septal defect, TOF: tetralogy of fallot, DORV: double outlet right ventricle, GIT: gastro-intestinal tract, CDH: congenital diaphragmatic hernia, CTEV: congenital talipes equinovarus, PUV: posterior urethral valve

Discussion

This study emphasizes the role of routine third trimester ultrasound in detecting late evolving and previously undiagnosed fetal anomalies. The total incidence of congenital anomalies in this study was 2.26% and anomalies detected by third trimester

ultrasound was about one third of the total (0.70%). In a study conducted by Ficara et al, the incidence of fetal anomalies was 1.9% and 0.5% were detected for the first time at 35–37 weeks[4]. According to Manegold et al, the incidence of congenital anomalies was 1.9% and anomalies detected in third trimester was 0.87%[5]. Gonzalez et al found that of the total anomalies, 31.9% were diagnosed at 11-14 weeks and 36.8% new fetal malformations were found in second trimester and additional 31.3% structural abnormalities were found in the routine third trimester ultrasound scan[6]. This was similar to our study, where 31.1% anomalies were detected after 28 weeks. Drukker et al concluded that a congenital malformation was incidentally detected in 1 in 300 women in third-trimester growth scan, who have had a previous normal first and second trimester scan[7].

According to this study urogenital anomalies were the most common anomaly detected in third trimester (32.7%), followed by cardiovascular system (21.8%), CNS (16.3%) and thoracic anomalies (10.9%). In the study by Ficara et al, 50% of anomalies in third trimester was in genito-urinary system and 27.5% in CNS[4]. According to Drukker et al, genitourinary system anomalies were the commonest followed by central nervous system[7]. Gonzalez et al found that structural abnormalities detected in the routine third trimester ultrasound were mainly in the urogenital system, followed by cardiovascular system and central nervous system[6].

Hydronephrosis was the commonest anomaly detected by third trimester ultrasound with an incidence of 1.2 per 1,000 births. In majority of the cases the condition remained stable or resolved in the neonatal period. Studies by Ficara et al and Drukker et al also showed that the commonest anomaly detected in the third trimester was hydronephrosis[4, 7]. According to Shipp et al, a new renal abnormality was detected in 1.8% of the third trimester scans when second trimester sonographic examination was normal[8]. Manegold et al found newly detected congenital structural abnormalities in the third trimester, of which 18 were urogenital anomalies mainly hydronephrosis[5].

The most common cardiac anomaly in this study was VSD. Gestational diabetes mellitus was seen in 29.16% of the mothers with babies having cardiac anomalies. According to Manegold et al, the second largest group of anomalies detected in third trimester was cardiovascular system mainly small muscular VSD[5]. In the study by Ficara et al of the cases of ventricular septal defect, 18.3% were first diagnosed in the third trimester and 4.2% were diagnosed postnatally[4]. Cardiovascular anomalies like TOF, typically diagnosed in the mid trimester scans (18 – 22 weeks) were detected later in our study. This delayed detection may be attributed to the limited access to 3D or 4D ultrasonography for anomaly screening and fetal echocardiography being restricted to high-risk cases. Additionally, maternal obesity might have contributed to the late detection of these anomalies.

CNS anomalies detected after 28 weeks was 16.3% in this study of which dysgenesis of corpus callosum and ventriculomegaly were the commonest. In a study conducted by Yinon et al, 47 women were diagnosed with CNS anomalies after 24 weeks of gestation which included intracranial cysts, mild ventriculomegaly, absence or dysgenesis of the corpus callosum, and intracerebral haemorrhage[9]. The study by Vijayakumar et al showed that more than 50% anomalies first detected in the third trimester were in central nervous system and urogenital system[10].

Duodenal atresia was the commonest gastrointestinal anomaly detected. Ficara et al found that the most common gastrointestinal abnormality seen at 35–37 weeks was an abdominal cyst[4]. In this study, most of the GI anomalies were correctable with survival in 4 out of 5 newborns who underwent immediate surgery. Even though mortality rate of bowel atresia and anorectal malformations is very high, their outcome may improve, by promoting antenatal diagnosis, early diagnostic and therapeutic management[11].

Vijayakumar et al detected a case of eventration of diaphragm in third trimester with unremarkable postnatal period[10]. In this study, 50% of babies with CDH survived after surgical repair. The study by Chukwu et al showed that estimates of postnatal survival of CDH babies was 70%[12]. This emphasize the importance of antenatal detection of structural anomalies even in late pregnancy which helps parents and doctors to plan delivery and further management of the newborn.

CTEV was the most common skeletal anomaly followed by achondroplasia. Schram et al detected four cases of achondroplasia in third trimester[3]. There was one baby with Binders syndrome in whom mother had history of deep vein thrombosis and warfarin intake in first trimester.

73.6% of study population were between 20 -30 years of age and 20% were above 30 years. This was comparable to the study by Desai and Desai, where women less than 20 years had no babies with congenital anomalies and 73% of mothers with anomalous babies were between 20 and 30 years and 26.7% were above 30 years[13]. Other studies by Taksande et al and Desai et al also found statistically significant association of increasing maternal age and congenital anomalies[14,15].

24.5% of study population had history of previous abortion and 3.6% had previous still birth or neonatal deaths and 2.7% had previous anomalous babies. Thaddanee et al concluded that congenital anomalies in newborns were significantly associated with maternal factors like maternal age, consanguinity, previous child with malformation, history of previous abortion and severe anemia[16].

13.6% of study population had polyhydramnios and 14.5% had oligohydramnios. Wills et al concluded that the common obstetric problems identified in congenital anomalies included oligohydramnios and polyhydramnios[16].

As in studies by Desai et al and Wills et al which showed increased incidence of anomalies among male babies[13, 17]. 58.1% of babies in this study were males. According to Daizy et al, congenital malformation and gender was found to be statistically significant with male preponderance[18]. The reason for greater numbers in male population is thought to be caused by the fact that male embryos are more vulnerable to oxidative stress which could partly be explained by the biological fragility of the male embryo. Oxidative stress has been implicated in the pathogenesis of several congenital anomalies[19].

Our institution being a tertiary care centre, all the referred cases with anomalies detected in third trimester could be included in the study. Serial ultrasound scans from the fetal medicine unit and postnatal evaluation and interventions from the neonatology and paediatric surgery department could be closely followed-up. Limitation of the study was that some of the major anomalies detected in the third trimester may be due to improper targeted anomaly scan.

Conclusion

It is essential to include third trimester scan in our regular antenatal protocol and should be considered as "more than growth scan". Anomalies detected in third trimester will have lot of bearing on psychological, ethical, social and legal implications. Counselling these couple is crucial and should include selection of timing and place of delivery and postnatal investigations. It also helps to plan for neonatal intervention which potentially improve the postnatal outcome.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Effectiveness of Lidocaine Spray Combined with Oral Paracetamol versus Oral Paracetamol Alone for Pain Reduction in Diagnostic Amniocentesis: A randomized controlled trial

Nattakan Jirattitipat, M.D.*,
Metha Songthamwat, M.D., Ph.D.*

** Department of Obstetrics and Gynecology, Udonthani Hospital, Udon Thani, Thailand*

ABSTRACT

Objectives: To determine whether lidocaine spray at the amniocentesis puncture site, combined with oral paracetamol, reduced procedural pain compared with paracetamol alone.

Materials and Methods: We conducted a randomized, double-blind, placebo-controlled trial at a tertiary care hospital (August 2024–June 2025). A total of 192 pregnant women undergoing diagnostic amniocentesis were randomized equally into two groups. The intervention group (n = 96) received 10% lidocaine spray, and the control group (n = 96) received placebo spray identical in appearance. All participants received oral paracetamol. Pain intensity at needle insertion (visual analog scale (VAS), 0–10) was the primary outcome. Secondary outcomes included VAS at other time points (during aspirate amniotic fluid and needle withdrawal, 15 and 30 minutes), maternal anxiety (State-Trait Anxiety Inventory), and satisfaction.

Results: Baseline characteristics were comparable between groups. Pain scores were significantly lower in the lidocaine group at needle insertion (median 4, interquartile range (IQR) 2–5 vs 5, IQR 3–6, p = 0.016), needle withdrawal (median 2, IQR 0–3 vs 3, IQR 1–5, p = 0.003), at 15 minutes (median 0, IQR 0–2 vs 0.5, IQR 0–3, p = 0.031), and at 30 minutes (median 0, IQR 0–1 vs 0, IQR 0–1.5, p = 0.091). Anxiety scores were similar between groups, whereas satisfaction scores were higher in the lidocaine group (mean ± standard deviation = 4.40 ± 0.67 vs 4.06 ± 0.77).

Conclusion: Lidocaine spray combined with oral paracetamol significantly reduced pain during and immediately after the procedure, and increased maternal satisfaction. This simple, safe, and low-cost approach may enhance maternal comfort during diagnostic amniocentesis.

Keywords: diagnostic amniocentesis, pain management, lidocaine, acetaminophen, satisfaction, anxiety.

Correspondence to: *Metha Songthamwat, M.D., Department of Obstetrics and Gynecology, Udonthani Hospital, Udon Thani 41000, Thailand. E-mail: Udonhome@yahoo.com*

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ประสิทธิผลของการใช้สเปรย์ลิโดเคนร่วมกับพาราเซตามอลชนิดรับประทานเปรียบเทียบกับการใช้พาราเซตามอลเพียงอย่างเดียวในการลด ความปวดระหว่างการเจาะน้ำคร่ำเพื่อวินิจฉัย: การศึกษาเชิงทดลองแบบสุ่มมีกลุ่มควบคุม

ณัฐกานต์ จิรัฐิติภัทร์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

***วัตถุประสงค์**: เพื่อประเมินว่าการพ่นสเปรย์ลิโดเคนบริเวณตำแหน่งเจาะน้ำคร่ำร่วมกับการรับประทานพาราเซตามอลสามารถลดความปวดขณะทำการเจาะน้ำคร่ำเมื่อเทียบกับการใช้พาราเซตามอลเพียงอย่างเดียวหรือไม่*

***วัสดุและวิธีการ**: ดำเนินการศึกษาแบบสุ่ม มีกลุ่มควบคุม และปกปิดสองทางในโรงพยาบาลตติยภูมิ ระหว่างเดือนสิงหาคม พ.ศ. 2567 ถึงมิถุนายน พ.ศ. 2568 โดยหญิงตั้งครรภ์ที่มีข้อบ่งชี้ในการเจาะน้ำคร่ำจำนวน 192 ราย ถูกสุ่มแบ่งออกเป็น 2 กลุ่มเท่า ๆ กัน กลุ่มทดลอง (จำนวน 96 คน) ได้รับสเปรย์ลิโดเคนร้อยละ 10 และกลุ่มควบคุม (จำนวน 96 คน) ได้รับสเปรย์น้ำเกลือที่มีลักษณะภายนอกเหมือนกัน ผู้เข้าร่วมทุกคนได้รับพาราเซตามอลชนิดรับประทานก่อนหัตถการ ตัวชี้วัดหลักคือระดับความปวดขณะแทงเข็มเจาะน้ำคร่ำวัดด้วยมาตราการให้คะแนนความปวด (Visual analog scale, 0–10) ตัวชี้วัดรองประกอบด้วยค่าคะแนนความปวดในช่วงเวลาอื่นๆ (ขณะดูดน้ำคร่ำ หลังทำหัตถการทันที 15 และ 30 นาที), ระดับความวิตกกังวลโดยใช้แบบสอบถาม State-Trait Anxiety Inventory และความพึงพอใจของผู้ป่วย*

***ผลการศึกษา**: ลักษณะพื้นฐานของผู้เข้าร่วมทั้งสองกลุ่มมีความใกล้เคียงกัน คะแนนความเจ็บปวดในกลุ่มที่ได้รับลิโดเคนต่ำกว่าอย่างมีนัยสำคัญทางสถิติในช่วงการแทงเข็ม (ค่ามัธยฐาน 4, พิสัยระหว่างควอร์ไทล์ 2–5 เทียบกับ 5, 3–6, p = 0.016), ช่วงถอนเข็ม (ค่ามัธยฐาน 2, พิสัยระหว่างควอร์ไทล์ 0–3 เทียบกับ 3, 1–5, p = 0.003), ที่ 15 นาทีหลังทำหัตถการ (ค่ามัธยฐาน 0, พิสัยระหว่างควอร์ไทล์ 0–2 เทียบกับ 0.5, 0–3, p = 0.031) และที่ 30 นาที (ค่ามัธยฐาน 0, พิสัยระหว่างควอร์ไทล์ 0–1 เทียบกับ 0, 0–1.5, p = 0.091) คะแนนความวิตกกังวลไม่แตกต่างกันระหว่างกลุ่ม ในขณะที่คะแนนความพึงพอใจของผู้ป่วยในกลุ่มที่ได้รับลิโดเคนสูงกว่า (ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน = 4.40 ± 0.67 เทียบกับ 4.06 ± 0.77)*

***สรุป**: การใช้สเปรย์ลิโดเคนร่วมกับพาราเซตามอลชนิดรับประทานช่วยลดความปวดได้อย่างมีนัยสำคัญ ทั้งในขณะทำและหลังการทำหัตถการในช่วงแรก รวมทั้งความพึงพอใจของผู้รับบริการที่เพิ่มขึ้น วิธีนี้มีความเรียบง่าย ปลอดภัย ราคาถูก และอาจใช้เป็นแนวทางที่เหมาะสมเพื่อเพิ่มความพึงพอใจของมารดาขณะทำการเจาะน้ำคร่ำ*

***คำสำคัญ**: การเจาะน้ำคร่ำเพื่อวินิจฉัย, การจัดการความปวด, ลิโดเคน, พาราเซตามอล, ความพึงพอใจ, ความวิตกกังวล*

Introduction

Diagnostic amniocentesis is among the most widely performed invasive procedures in obstetrics. All steps of the procedure are essential and must be performed with great care especially in pregnant women with specific conditions, such as those who are obese or taking antiplatelet medication or infected with human immunodeficiency virus (HIV), hepatitis B, etc. It involves transabdominal aspiration of amniotic fluid for prenatal diagnostic or therapeutic purposes, most commonly in the second trimester. The procedure is routinely indicated for suspected chromosomal abnormalities, severe thalassemia, and intrauterine infections, and continues to play a critical role in prenatal care despite the increasing availability of non-invasive prenatal testing (NIPT)[1-4].

Although considered safe, amniocentesis is not a pain-free procedure. Harris et al reported a mean pain score of 1.6 ± 1.3 (0–7 scale), with nearly one-third of women experiencing moderate to severe discomfort[5]. Pain perception may be influenced by maternal anxiety, history of dysmenorrhea, prior amniocentesis, and puncture site[6,7]. Various strategies for pain relief have been investigated, including subcutaneous lidocaine infiltration, lidocaine spray, topical anesthetic creams, oral paracetamol, and cold application[8-11]. Their efficacy, however, remains inconsistent. Subcutaneous infiltration with 1% lidocaine was reported ineffective in several trials[8,9], a finding supported by a meta-analysis[12]. In contrast, Elimian et al demonstrated that subcutaneous lidocaine significantly reduced pain[13]. Lidocaine spray has shown benefit in some studies[14]. Oral paracetamol and cold application have demonstrated modest benefit in selected trials[15-17].

Most interventions to date primarily address pain from skin puncture, while evidence on strategies that alleviate discomfort during uterine entry remains limited. Moreover, no study has evaluated the combined effect of lidocaine spray with systemic analgesics. At Udonthani Hospital, over 700 diagnostic amniocenteses are performed annually, highlighting the clinical importance of optimizing patient comfort. This study therefore aimed to evaluate the effectiveness of lidocaine spray combined with oral paracetamol compared with oral paracetamol alone in reducing procedural pain and improving patient satisfaction during diagnostic amniocentesis.

Materials and Methods

This study was a randomized, double-blind, placebo-controlled trial conducted at Udonthani Hospital, Thailand between August 2024 and June 2025. Eligible participants were pregnant women aged ≥ 20 years, at 16–22 weeks' gestation, with a medical indication for diagnostic amniocentesis. Exclusion criteria included hypersensitivity to lidocaine or paracetamol, local infection at the puncture site, multiple gestation, HIV infection, threatened miscarriage with ongoing pain or bleeding, unexplained vaginal bleeding, thrombocytopenia, or known coagulation disorder. The study protocol was reviewed and approved by the Udonthani Hospital Ethical Committee in Human Subject Research (No. 127/2567).

The study protocol was explained in detail to eligible participants and their spouses or relatives, including the necessity of the procedure, potential complications, risk of fetal loss, procedural steps, post-procedural care, timeline for result reporting, and study participation. Written informed consent was obtained from all participants.

Participants were randomized in a 1:1 ratio to intervention (lidocaine spray + paracetamol) or control (placebo spray + paracetamol) using a computer-generated sequence, with allocation concealed in sequentially numbered opaque envelopes. The study sprays, prepared and labeled by a pharmacist not involved in the procedures, were identical in appearance. Both participants and operators were blinded to group allocation.

All women received 500 mg oral paracetamol one hour before amniocentesis. In the intervention group, 10% lidocaine spray was applied eight times at the predetermined puncture site, identified by pre-

procedure ultrasound, five minutes before the procedure. The control group received an identical placebo spray (normal saline) applied in the same manner.

All procedures were performed by maternal-fetal medicine specialists under aseptic conditions using ultrasound-guided transabdominal amniocentesis. A pre-procedure ultrasound was performed to confirm gestational age, placental location, cord insertion, amniotic fluid pocket, and to determine the optimum puncture site for spray application. A 22-guage spinal needle was then inserted and advanced into the selected pocket, and amniotic fluid was aspirated for laboratory analysis.

The primary outcome was mean procedural pain after needle insertion, measured using the visual analog scale (VAS, 0–10). Secondary outcomes included pain scores at other standardized time points (after spray application, during aspiration of amniotic fluid, needle withdrawn, 15 minutes post-procedure, and 30 minutes post-procedure), patient satisfaction with pain management, and immediate complications (e.g., vaginal bleeding, uterine cramping). Anticipated pain and anxiety prior to the procedure were also assessed using the validated Thai version of the State-Trait Anxiety Inventory (STAI)[18,19], a standardized self-reported questionnaire used to measure state anxiety levels.

Participants were monitored for 30 minutes post-procedure before discharge with standard post-procedure advice. The VAS is a validated tool for measuring pain intensity, consisting of a 10-cm line anchored with "0 = no pain" and "10 = worst pain imaginable," on which participants indicate their perceived pain level[20].

The required sample size was estimated for comparing mean pain scores between two independent groups using the n4 Studies application. Based on data from Homkrun et al[21], the mean pain score was 2.3 (standard deviation (SD) 1.8) in the treatment group and 3.3 (SD 3.3) in the control group, with a 1:1 allocation ratio. With $\alpha = 0.01$ (two-tailed) and $\beta = 0.20$ (80% power), the calculated sample size was 87 participants per group. Allowing for a 10% dropout rate, 96 participants were required per group, yielding a total sample size of 192 (96 in the lidocaine spray plus paracetamol group and 96 in the paracetamol only group). Data were analyzed using Stata version 13 (StataCorp LP, College Station, TX, USA). Continuous variables were tested for normality using the Shapiro–Wilk test and summarized as mean with SD or median with interquartile range (IQR), as appropriate. Categorical variables were presented as frequencies and percentages.

The primary outcome (mean or median procedural pain score, VAS 0–10) was compared between groups using the independent-samples t-test or Mann–Whitney U test, as appropriate. Secondary outcomes included pain scores at 15- and 30-minutes post-procedure, maternal satisfaction, and immediate complications. Pain and satisfaction scores were analyzed using the same approach as the primary outcome. Categorical outcomes, such as complication rates, were compared using Pearson's chi-square test or Fisher's exact test. A p value < 0.05 was considered statistically significant.

Results

A total of 192 pregnant women were enrolled in the study, and none were excluded. Of these, 96 women were randomly allocated to the lidocaine spray plus paracetamol group, and 96 women were allocated to the placebo spray plus paracetamol group. No participants were excluded based on the predefined criteria. The study flow is summarized in Fig. 1.

The demographic and clinical characteristics of participants are presented in Table 1. There were no statistically significant differences between the two groups with respect to age, body mass index (BMI), parity, previous amniocentesis, underlying diseases (including diabetes mellitus, hypertension), or indications for diagnostic amniocentesis.

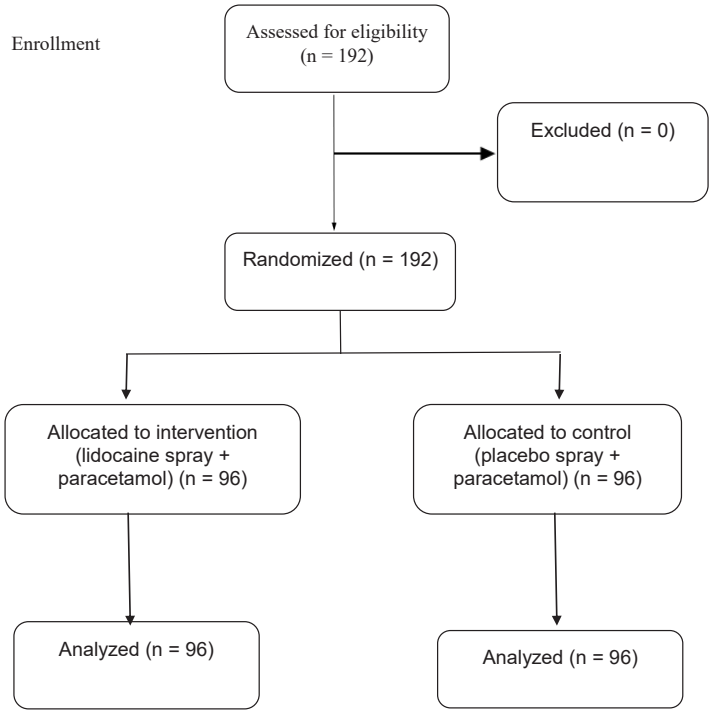

Fig. 1. CONSORT flow diagram of participant enrollment, allocation, and analysis.

Table 1. Baseline maternal and clinical characteristics of participants by study group.

Characteristics	Lidocaine spray + paracetamol (n = 96)	Placebo spray + paracetamol (n = 96)	p value
Age (years), median (IQR)	33 (28, 37)	33 (27, 37)	0.915
Gestational age (weeks), median (IQR)	19 (19, 19)	19 (19, 19)	0.949
Multiparity, n (%)	78 (81.25%)	73 (76.04%)	0.379
Previous history of amniocentesis, n (%)	11(11.46%)	7 (7.29%)	0.322
Body mass index (kg/m^2), median (IQR)	25.34 (22.94, 27.64)	24.54 (21.96, 28.35)	0.442
Underlying disease, n (%)			
Diabetes Mellitus	11 (11.46%)	8 (8.33%)	0.468
Hypertension	1 (1.04%)	4 (4.17%)	0.368
Other disease	7 (7.29%)	12 (12.50%)	0.227
Indication of diagnostic amniocentesis, n (%)			
High-risk quadruple test	82 (85.26%)	83 (86.44%)	0.836
Other	14 (14.58%)	13 (13.54%)	
Operation time (minutes), median (IQR)	2 (1,3)	1 (1,2)	0.229

IQR: interquartile range

p values were calculated using Man Whitney U test for continuous variables, Pearson's chi-square test for categorical variables, and Fisher's exact test when expected counts < 5.

The primary and secondary outcomes are summarized in Table 2. Pain scores during and after diagnostic amniocentesis were consistently lower in the lidocaine spray group compared with the placebo group. The pain score during needle insertion were significantly lower in the lidocaine group (p = 0.016). Pain scores during and after diagnostic amniocentesis are summarized in Table 2. The lidocaine spray group reported significantly lower pain than the placebo group at several time points, including after needle insertion (primary outcome), needle withdrawal and at 15 minutes post-procedure. Overall, topical lidocaine spray provided a relevant reduction in pain, particularly at the time of needle insertion and in the early post-procedure period.

Anxiety and satisfaction outcomes are presented in Table 3. Anxiety levels, both before and after the procedure, were comparable between the lidocaine and placebo groups, indicating that the intervention did not significantly influence maternal anxiety. However, patients who received lidocaine spray reported higher satisfaction with pain management compared with those in the placebo group.

Table 2. Pain scores during and after diagnostic amniocentesis.

Outcome	Lidocaine spray group (n = 96)	Placebo group (n = 96)	p value
Pain score after spray application, median (IQR)	0 (0,0)	0 (0,0)	0.049
Pain score during needle insertion, median (IQR)	4 (2,5)	5 (3,6)	0.016
Pain score during aspirate amniotic fluid, median (IQR)	3 (1,5)	4 (1.5,6)	0.053
Pain score during needle withdrawal, median (IQR)	2 (0,3)	3 (1,5)	0.003
Pain score 15 minutes post-procedure, median (IQR)	0 (0,2)	0.5 (0,3)	0.031
Pain score 30 minutes post-procedure, median (IQR)	0 (0,1)	0 (0,1.5)	0.091

IQR: interquartile range

p values were calculated using Mann-Whitney U test

Table 3. Anxiety scores measured with the State-Trait Anxiety Inventory (STAI) and satisfaction with pain management during diagnostic amniocentesis.

Outcome	Lidocaine spray group (n = 96)	Placebo group (n = 96)	Mean difference (95%CI)
Pre-procedure anxiety score (STAI), mean ± SD	41.68±9.10	40.98±7.71	0.70 (-1.70 to 3.10)
Post-procedure anxiety score (STAI), mean ± SD	37.55±8.78	38.36±10.25	-0.81(-3.53 to 1.90)
Patient satisfaction score, mean ± SD	4.40±0.67	4.06±0.77	0.33 (0.13 to 0.54)

STAI: State-Trait Anxiety Inventory; CI: confidence interval; SD: standard deviation

p values were calculated using Mann-Whitney U test

Discussion

This randomized controlled trial evaluated the effect of combining lidocaine spray with oral paracetamol on maternal pain, anxiety, and satisfaction during diagnostic amniocentesis. The intervention significantly reduced pain intensity after needle insertion (primary outcome), needle withdrawal, and at 15-minutes post-procedure compared with paracetamol alone. Maternal satisfaction was also higher in the lidocaine group, whereas pre- and post-

procedure anxiety scores were not significantly different.

Previous trials have primarily investigated systemic or local analgesic strategies separately. Systemic agents such as oral paracetamol were shown to significantly reduce procedural pain compared with placebo in studies by Tuaktaew et al[22]. Local anesthetic approaches have also been evaluated, including lidocaine-prilocaine cream by Pongrojpaw et al[23], subcutaneous lidocaine infiltration by Elimian et al[12] and Gordon et al[8], and lidocaine spray by Sriwattanapong et al[24] and Homkrun et al[21]. While some of these trials demonstrated significant analgesic effects, others yielded inconclusive results, and a Cochrane review by Mujezinovic et al[10] in 2011 concluded that there is insufficient evidence to support the use of local anesthetics.

Our study extends this evidence by evaluating a combination strategy, in which a systemic analgesic (oral paracetamol) was supplemented with a local anesthetic (lidocaine spray). This dual approach resulted in greater pain reduction than paracetamol alone, particularly at needle insertion and in the immediate and early post-procedure phases. These results are comparable in magnitude to or greater than the effects observed in prior single-agent studies, suggesting a potential synergistic benefit when systemic and local modalities are combined.

The observed analgesic benefit is biologically plausible given the complementary mechanisms of the two agents: paracetamol provides systemic central analgesia, while lidocaine spray offers localized, immediate relief at the puncture site. Together, these modalities may enhance maternal comfort during amniocentesis.

Importantly, variability in baseline VAS scores across trials highlights that maternal pain perception during amniocentesis is influenced not only by the choice of analgesic but also by cultural factors, baseline anxiety, procedural technique, and operator experience. Nevertheless, our findings support the concept that combining systemic and local analgesic approaches can enhance maternal comfort beyond what is achieved by systemic agents alone.

Regarding anxiety, our study found no significant differences between groups, a finding was consistent with previous literature indicating that maternal anxiety during invasive procedures is primarily influenced by psychological and contextual factors—such as concern about fetal outcomes and miscarriage risk—rather than procedural pain itself (Chua et al[25], and Lalor et al[26]. Non-pharmacological strategies, including counseling, relaxation techniques, or music therapy, have been shown to be more effective in reducing procedural anxiety than pharmacological interventions (Koivisto et al[27], and Bani-Issa et al[28]).

In contrast, maternal satisfaction scores were significantly higher in the lidocaine group. This finding was in line with Shen et al[29], who reported that satisfaction after invasive obstetric procedures was closely associated with pain management and perceived comfort, even when anxiety levels remained unchanged. Taken together, these results suggest that while lidocaine spray does not directly alleviate maternal anxiety, its capacity to reduce procedural pain is sufficient to improve maternal satisfaction, underscoring its clinical relevance.

The strengths of this study included its randomized, double-blind, placebo-controlled design, an adequately powered sample size, and the use of validated instruments to assess anxiety, and satisfaction. These methodological features enhanced the internal validity and reliability of the findings.

Nevertheless, several limitations should be acknowledged. First, the trial was conducted at a single tertiary-care center, which may limit the generalizability of the results to other populations or healthcare settings. Second, the study focused primarily on short-term outcomes and did not evaluate long-term psychological effects, such as persistent anxiety or subsequent attitudes toward invasive procedures. Third, pain assessment relied on self-reported scales, which were inherently subjective and

may vary according to individual pain thresholds, cultural factors, and emotional state. Future multicenter studies with mixed-methods approaches are warranted to address these gaps and further establish the external validity and clinical applicability of the findings.

From a clinical perspective, the use of lidocaine spray in combination with oral paracetamol represents a simple, low-cost, and well-tolerated strategy to improve maternal comfort during diagnostic amniocentesis. Integrating this dual method into routine practice could enhance patient satisfaction and acceptance of the procedure without adding substantial burden to clinical workflow. Another interesting approach is the combination with cryoanalgesia, which provides a localized effect, is reusable and carries a low risk of adverse effects[30]. For future research, larger multicenter randomized trials are needed to confirm the reproducibility of these findings across diverse populations and healthcare systems. Studies evaluating psychological outcomes, such as maternal anxiety, would provide further insight into patient-centered care. Incorporating qualitative assessments and exploring the role of non-pharmacological interventions in combination with pharmacologic analgesia may also yield a more comprehensive understanding of maternal experience during amniocentesis.

Conclusion

Combining lidocaine spray with oral paracetamol significantly reduced procedural pain during amniocentesis compared with paracetamol alone. While anxiety levels remained unchanged, maternal satisfaction was higher in the lidocaine group. Given its simplicity, safety, and low cost, this dual approach offers a practical strategy to improve maternal comfort during amniocentesis.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Impact of Obesity on Treatment and Survival Outcome in Epithelial Ovarian Cancer Patients: A 10-year retrospective study

Asavarak Sompohnmanas, M.D.*,
Irene Ruengkhachorn, M.D.*,
Nida Jareemit, M.D.*,
Khemanat Khemworapong, M.D.*,
Vuthinun Achariyapota, M.D.*

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

ABSTRACT

Objectives: To assess the influence of women with obesity on surgical outcomes, chemotherapy side effects, and survival rates in Thai patients with epithelial ovarian cancer.

Materials and Methods: A retrospective review was conducted of the medical records of patients with epithelial ovarian cancer who underwent staging laparotomy at Siriraj Hospital between January 2008 and December 2017. Patients were categorized as patients without obesity (body mass index [BMI] < 25.0 kg/m^2) or patient with obesity (BMI ≥ 25 kg/m^2) according to the Western Pacific Regional Office BMI criteria. We compared patient demographics, surgical outcomes, chemotherapy complications, and survival data between the two groups.

Results: From an initial cohort of 444 patients, 18 were excluded, leaving 426 for analysis. The women with obesity group, representing 21.9% (n = 93) of the patients, exhibited a higher prevalence of diabetes mellitus (p < 0.0001), hypertension (p = 0.003), and dyslipidemia (p = 0.027) than the women without obesity group (78.1%, n = 333). Patients with obesity were significantly associated with increased postoperative complications, notably wound issues (adjusted odds ratio [OR] 6.175, 95% confidence interval [CI] 1.891–13.191; p < 0.001) and venous thromboembolism (adjusted OR 5.991, 95% CI 2.848–12.605; p < 0.001), but it correlated with fewer cases of neutropenia (p = 0.002) and reduced delays in chemotherapy (p = 0.015). There were no significant differences in progression-free survival (p = 0.135) or five-year overall survival (p = 0.923).

Conclusion: Thai women with obesity with epithelial ovarian cancer was linked to an increased risk of postoperative complications, increased chemotherapy tolerability, but did not affect survival outcomes.

Keywords: obesity, ovarian cancer, wound complication, thromboembolism, survival

Correspondence to: *Vuthinun Achariyapota, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: vuthinun.ach @mahidol.edu*

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ผลกระทบของโรคอ้วนต่อการรักษาและผลลัพธ์การรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว: การศึกษาย้อนหลังระยะเวลา 10 ปี

อัศวรักษ์ สมพรมนัส, ไอรีน เรืองขจร, นิดา จารีมิตร, เขมณัฏฐ์ เขมวรพงศ์, วุฒินันท์ อัจฉริยะโพ

บทคัดย่อ

วัตถุประสงค์: *การศึกษานี้จัดทำเพื่อศึกษาความสัมพันธ์ระหว่างโรคอ้วนต่ออัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว และเพื่อศึกษาความสัมพันธ์ระหว่างโรคอ้วนต่อผลการผ่าตัดและการให้ยาเคมีบำบัดในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว*

วัสดุและวิธีการ: *เป็นการทบทวนเวชระเบียนย้อนหลังผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่ได้รับการรักษาผ่าตัดประเมินระยะของโรคและให้ยาเคมีบำบัด ระหว่างเดือน มกราคม พ.ศ. 2551- ธันวาคม พ.ศ.2561 ณ โรงพยาบาลศิริราช โดยเก็บข้อมูลลักษณะพื้นฐานของผู้ป่วย ข้อมูลระหว่างการผ่าตัด การให้ยาเคมีบำบัด รวมถึงผลข้างเคียงที่เกิดขึ้น ไปจนถึงระยะเวลาที่โรคกลับมาเป็นซ้ำ หรือระยะเวลาที่เสียชีวิต โดยแบ่งคนไข้เป็นกลุ่มจากการคำนวณค่าดัชนีมวลกาย (BMI) โดยแบ่งตามเกณฑ์ขององค์การอนามัยโลกภูมิภาคแปซิฟิกตะวันตก (Western Pacific Regional Office (WPRO) โดยกลุ่มโรคอ้วนคือมี ดัชนีมวลกาย BMI ≥ 25 กก./ม^2 และกลุ่มไม่มีโรคอ้วนคือ BMI < 25.0 กก./ม^2 เพื่อทำการเปรียบเทียบอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว ผลแทรกซ้อนระหว่างและหลังการผ่าตัดและผลข้างเคียงระหว่าการให้ยาเคมีบำบัดระหว่างสองกลุ่ม*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวทั้งหมด 426 คน แบ่งเป็นกลุ่มที่มีโรคอ้วนร้อยละ 21.9 (93 คน) กลุ่มไม่มีโรคอ้วนร้อยละ 78.1 (333 คน) โดยพบว่าในกลุ่มที่มีโรคอ้วน จะพบโรคประจำตัว เบาหวาน (p < 0.0001), ความดันโลหิตสูง (p = 0.003), และไขมันในเลือด (p = 0.027) มากกว่ากลุ่มที่ไม่มีโรคอ้วน โดยพบว่าโรคอ้วนในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว เพิ่มความเสี่ยงต่อการเกิดภาวะแทรกซ้อนของแผลผ่าตัด (adjusted odds ratio (OR): 6.175; 95% CI: 1.891-13.191; p < 0.001) และภาวะลิ่มเลือดอุดตันในหลอดเลือดดำหลังการผ่าตัด (adjusted OR: 5.991; 95% CI: 2.848-12.605; p < 0.001) ในด้านผลของโรคอ้วนต่อการให้ยาเคมีบำบัดพบว่า ในกลุ่มที่มีโรคอ้วนพบการมีเม็ดเลือดขาวต่ำหลังให้ยาเคมีบำบัดที่น้อยกว่า (p = 0.002) และการเลื่อนในการให้ยาเคมีบำบัดที่น้อยกว่า (p = 0.015) เมื่อเปรียบเทียบกับกลุ่มไม่มีโรคอ้วน โดยอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว (p = 0.135) และอัตราการอยู่รอดโดยโรคสงบใน 5 ปี (p = 0.923) ทั้งสองกลุ่มพบว่าไม่มีความแตกต่างมีนัยสำคัญทางสถิติ*

***สรุป**: โรคอ้วนไม่มีผลต่ออัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว แต่เพิ่มความเสี่ยงต่อภาวะแทรกซ้อนของแผลภายหลังการผ่าตัดและภาวะลิ่มเลือดอุดตันในหลอดเลือดดำหลังการผ่าตัด*

***คำสำคัญ**: โรคอ้วน, มะเร็งรังไข่, ภาวะแทรกซ้อนของแผลผ่าตัด, ภาวะลิ่มเลือดอุดตันในหลอดเลือด, อัตราการรอดชีวิต*

Introduction

The prevalence of women with obesity, which is increasingly recognized as a major global public health challenge, has increased markedly over the last decade. In Thailand, the prevalence of women with obesity (body mass index [BMI] ≥ 25 kg/m²) increased from 33.9% in 2012 to 44.8% in 2018[1]. This condition is associated with a higher incidence of several health issues, including cardiovascular diseases, diabetes mellitus, sleep apnea, arthritis, and various cancers[2, 3]. Notably, increased BMI has been linked to elevated mortality in women with cancers specific to the breast, uterus, cervix, or ovaries[4, 5]. Prior studies suggest that obesity may contribute to poorer survival in epithelial ovarian cancer through alterations in tumor biology. For instance, Pavelka et al hypothesized that the elevated mortality observed in obese patients is attributable to more aggressive tumor characteristics[6].

Ovarian cancer is the seventh most common cancer among Thai women and ranks third among gynecologic malignancies, trailing only cervical and endometrial cancers[7]. It remains the most lethal gynecologic cancer in Thailand, and its challenging prognosis is reflected in a 30%–50% five-year survival rate following diagnosis[8].

For ovarian cancer, the standard treatment protocol includes cytoreductive debulking surgery and adjuvant chemotherapy. The primary goal of debulking surgery in ovarian cancer treatment is extensive removal of the tumor. This procedure aims to achieve a residual tumor size that is either microscopic or does not exceed 1 cm in maximum diameter, a criterion defined as “optimal” by the Gynecologic Oncology Group. Studies indicate that achieving this optimal surgical standard, followed by adjuvant chemotherapy, significantly improves patient outcomes and survival rates[9]. However, the presence of obesity has been linked to challenges in achieving optimal outcomes in cytoreductive surgery. These challenges include prolonged surgery durations, increased intraoperative blood loss, and a heightened risk of wound complications in patients with obesity[10, 11]. Furthermore, chemotherapy treatment in individuals with obesity often involves dosing based on ideal body weight. This approach may lead to an underestimation of the glomerular filtration rate using standard formulas, resulting in suboptimal chemotherapy dosages and potentially diminished treatment effectiveness[12, 13]. Although some studies have identified women with obesity as an independent prognostic factor for ovarian cancer survival, the scientific community has not reached a consensus on this relationship[11, 14-16].

This study evaluated the impact of patients with obesity on surgical outcomes (including intraoperative and postoperative complications), the adverse effects of chemotherapy, and survival rates in Thai patients diagnosed with epithelial ovarian cancer.

Materials and Methods

This retrospective, single-center cohort study spanned a 10-year period at Siriraj Hospital, Mahidol University, Bangkok, Thailand. Institutional Review Board approval was obtained (approval number SI-018/2022), permitting the review of medical records of 444 patients who attended the Division of Gynecologic Oncology between January 1, 2008, and December 31, 2017.

This study included patients diagnosed with epithelial ovarian cancer who underwent staging laparotomy at Siriraj Hospital during the study period. Excluded were individuals with nonepithelial ovarian cancer, borderline tumors, simultaneous primary malignancies, or other cancer types potentially influencing survival outcomes. Additionally, patients lacking recorded height and weight data were omitted.

The collected data included demographic and clinical information: underlying disease, age at diagnosis, disease stage, initial cancer antigen 125 (CA 125) level, and surgical outcome. We also recorded intraoperative and postoperative complications within 30 days, side effects from chemotherapy, and survival rates. This comprehensive data collection aimed to evaluate the impact of women with obesity on these outcomes among patients with epithelial ovarian cancer.

Body weight was measured upon admission for the first cycle of chemotherapy following surgical staging, or before receiving the first cycle of neoadjuvant chemotherapy. Body mass index was calculated using these weight and height measurements according to this formula: BMI = weight (kg) ÷ height^2 (meters). Considering our Thai study population, we adopted the Western Pacific Regional Office guidelines, which define women with obesity as a BMI ≥ 25 kg/m^2, instead of the World Health Organization's threshold of ≥ 30 kg/m^2. Accordingly, patients were categorized into women without obesity (BMI < 25 kg/m^2) and women with obesity (BMI ≥ 25 kg/m^2) groups.

For disease status, underlying conditions were recorded at the time of diagnosis of epithelial ovarian cancer. The initial CA 125 level was determined before surgical staging or the initiation of neoadjuvant chemotherapy. Surgical staging defined as women who underwent exploratory laparotomy for at least salpingo-oophorectomy of affected ovary and/or hysterectomy or pelvic lymphadenectomy or omentectomy.

The operation time encompassed the duration from surgery commencement to completion. Optimal cytoreductive surgery was considered to have been achieved when residual tumor was either nonexistent or measured 1 cm or less.

Postoperative complications were defined in specific terms. Fever defined as an oral (or equivalent) body temperature of 100.4 °F (38 °C) or greater, occurring on two separate postoperative days, excluding the first 24 hours after surgery[17]. Gastrointestinal complications included bowel ileus and bowel obstruction that necessitated treatment. Respiratory complications encompassed postoperative atelectasis and pneumonia. Wound problems were identified as complications, including infections, occurring at the surgical wound sites on the abdomen and vaginal stump. Venous thromboembolism was defined as confirmed pulmonary embolism and deep vein thrombosis in the lower limbs. Any serious events requiring immediate treatment during the hospital stay or within 30 days after surgery were also considered.

In documenting chemotherapy side effects, we deemed severe adverse hematologic events as thrombocytopenia (platelet count < 100,000 platelets per microliter.), neutropenia (absolute neutrophil count < 1,500 neutrophils per microliter), or anemia

(hemoglobin < 10 grams per deciliter). Liver toxicity was defined as an increase in aspartate aminotransferase or alanine aminotransferase levels to more than twice the upper normal limit. Peripheral neuropathy was assessed using grade I or higher of the World Health Organization grading scale. Treatment delays, dose reductions, and permanent discontinuations due to chemotherapy toxicity were also recorded.

Disease recurrence was identified by abnormal findings in physical or per-vaginal examinations, and unusual results from computed tomography scans and/or elevated tumor markers such as CA 125 or CA 19-9, progression-free survival (PFS) and overall survival (OS) were calculated from the time of diagnosis to the date of recurrence, death, or the most recent follow-up, whichever came first.

The required sample size was determined based on the primary objective of evaluating the association between obesity and survival outcomes in patients with epithelial ovarian cancer at Siriraj Hospital. A previous study by Zhang et al reported mortality rates of 28%, 45%, 44%, and 65% among underweight, normal, overweight, and obese groups, respectively, with statistically significant differences across BMI categories. Using these findings, the sample size calculation was performed with a two-sided significance level of 0.05 (type I error = 5%) and a power of 90% (type II error = 10%), indicating a minimum of 52 patients per group. To estimate feasibility, a pilot study of 50 patients with epithelial ovarian cancer treated at Siriraj Hospital was reviewed, which demonstrated that 14% of patients were classified as underweight, representing the smallest subgroup. Based on this distribution, the total study population required was approximately 370 patients. To account for an anticipated 20% rate of incomplete or missing data, the final sample size was set at 444 patients.

The statistical analyses in this study were performed using IBM SPSS Statistics version 29 (SPSS Inc, Chicago, IL, USA) for Windows® version 29. For demographic data, quantitative variables with a normal distribution were summarized as the mean ± standard deviation, while those with a nonnormal distribution were expressed as the median and interquartile range. Group comparisons of these variables were conducted using the independent t test and the Mann–Whitney U test. Categorical variables are reported as frequencies and percentages and were analyzed using either the chi-square test or Fisher's exact test, depending on appropriateness. The Kaplan–Meier method was employed to estimate PFS and OS. Statistical significance was defined as p-values less than 0.05.

Results

Initially, data from 444 patients were gathered. However, 18 of these patients were excluded due to missing data or the presence of dual primary cancers, resulting in a final cohort of 426 patients. The demographic and clinical details of the participants are summarized in Table 1.

The study included 93 (21.9%) patients with obesity and 333 (78.1%) patients without obesity. The groups were similar in terms of age, age at diagnosis, disease stage, and initial CA 125 concentration. However, the patients with obesity had a higher prevalence of diabetes mellitus (21.5% vs 8.4%, $p < 0.001$), hypertension (37.6% vs 22.2%, $p = 0.003$), and dyslipidemia (18.3% vs 9.9%, $p = 0.027$) (Table 1).

The patients with obesity and patients without obesity showed no significant differences in histopathological characteristics. These included histology, grade, lymph node counts, positive lymph nodes harvested, omental involvement, and malignant cells in peritoneal washings (Table 1).

Table 1. Demographic and clinical data of patients undergoing epithelial ovarian cancer surgery of 426 patients.

	Total Number	Patients without obesity (n = 333)	Patients with obesity (n = 93)	p value
Mean age at diagnosis (year)	54.18 ± 10.71	54.91 ± 10.60	54.33 ± 11.18	0.649
BMI (kg/m^2)	23.58 ± 0.35	20.49 ± 0.35	28.74 ± 0.17	< 0.0001
Underlying diseases				
Cardiovascular	20 (4.7%)	16 (4.8%)	4 (4.3%)	1.000
Diabetes mellitus	48 (11.3%)	28 (8.4%)	20 (21.5%)	< 0.001
Hypertension	109 (25.6%)	74 (22.2%)	35 (37.6%)	0.003
Dyslipidemia	50 (11.7%)	33 (9.9%)	17 (18.3%)	0.027
FIGO stage				0.555
I	183 (43%)	140 (42%)	43 (46.2%)	
II	38 (8.9%)	28 (8.4%)	10 (10.8%)	
III	153 (35.9%)	121 (36.3%)	32 (34.4%)	
IV	52 (12.2%)	44 (13.2%)	8 (8.6%)	
Initial CA 125 (units/mL)	206.5 [67.6–833.5]	201.8 [68.1–832]	226 [63.7–1025.5]	0.892
Histology				0.703
Clear cell	159 (37.3%)	123 (36.9%)	36 (38.7%)	
Serous	136 (31.9%)	105 (31.5%)	31 (33.3%)	
Endometrioid	53 (12.4%)	42 (12.6%)	11 (11.8%)	
Mucinous	36 (8.5%)	26 (7.8%)	10 (10.8%)	
Adenocarcinoma	23 (5.4%)	21 (6.3%)	2 (2.2%)	
Others	19 (4.4%)	16 (4.8%)	3 (3.2%)	
Grading				0.072
1	36 (15.3%)	23 (12.5%)	13 (25.5%)	
2	59 (25.1%)	47 (25.5%)	12 (23.5%)	
3	140 (59.6%)	114 (62.0%)	26 (51%)	
No. of LN harvested	10 [4–17.5]	10 [3.25–17]	12 [5–18]	0.446
No. of positive LNs	0 [0–0]	0 [0–0]	0 [0–0]	0.318
Omental involvement	141 (36%)	112 (36.1%)	29 (35.4%)	0.898
Presence of malignant cells in peritoneal washing	118 (42.3%)	90 (41.3%)	28 (45.9%)	0.519

BMI: body mass index, FIGO: International Federation of Gynecology and Obstetrics, CA: cancer antigen, LN: lymph node

Regarding surgical treatment, no significant differences were observed between the groups in hospital stay duration, operation time, estimated blood loss, optimal debulking rates, or intraoperative complications. Nevertheless, the patients with obesity exhibited a greater incidence of wound complications (21.5% vs 4.2%, p < 0.001) and venous thromboembolism (4.3% vs 0.6%, p = 0.022) (Table 2). After adjusting for comorbidities and operation time, patients with obesity were independently associated with an increased risk of wound complications (adjusted odds ratio (OR) 6.175, 95% confidence interval (CI) 1.891–13.191; p < 0.001) and venous thromboembolism (aOR 5.991, 95% CI 2.848–12.605; p < 0.001).

Table 2. Clinical outcomes following epithelial ovarian cancer surgery of 426 patients.

	Total Number	**Patients without obesity (n = 333)**	**Patients with obesity (n = 93)**	**p value**
Hospital stays (days)	7 [6–11]	8 [6–11]	8 [6-11]	0.352
Operative time (hours)	2.99 ± 1.2	2.97 ± 1.2	3.04 ± 1.2	0.650
EBL (ml)	500 [300–1,000]	500 [300–1,000]	500 [300–1,000]	0.880
Optimal debulking	307 (72.1%)	240 (72.1%)	67 (72.1%)	0.811
Intraoperative complications				
- Tumor rupture	247 (58%)	188 (56.5%)	59 (63.4%)	0.228
- Blood transfusion	120 (28.2%)	94 (28.2%)	26 (28%)	0.959
- Bowel injury	27 (6.3%)	23 (6.9%)	4 (4.3%)	0.362
- Urological injury	7 (1.6%)	5 (1.5%)	2 (2.2%)	0.650
Postoperative complications				
- Wound problems	34 (8%)	14 (4.2%)	20 (21.5%)	< 0.001
- Fever	50 (11.7%)	35 (10.5%)	15 (16.1%)	0.137
- Gastrointestinal problems (ileus, gut obstruction)	8 (1.8%)	3 (4%)	1 (1%)	1.000
- Respiratory problems (atelectasis, pneumonia)	8 (1.8%)	7 (2.1%)	1 (1%)	1.000
- VTE (pulmonary embolism, deep vein thrombosis)	6 (1.4%)	2 (0.6%)	4 (4.3%)	0.022

EBL: estimated blood loss, VTE: venous thromboembolism

Data presented as mean ± standard deviation, median [interquartile range] or n (%)

For chemotherapy outcomes, the total number of chemotherapy cycles, the need for neoadjuvant therapy, and the incidence of side effects such as thrombocytopenia, anemia, liver toxicity, and neuropathy were similar in both groups. However, the patients with obesity group had a significantly lower incidence of neutropenia (30.1% vs 48.5%, p = 0.002) and significantly fewer chemotherapy delays (38.7% vs 53%, p = 0.015) (Table 3).

Of the 426 patients, 107 (25.1%) experienced disease recurrence, and 117 (27.4%) died. The median follow-up period was 49 months (interquartile range (IQR) 22.5–95.5) for the patients with obesity group and 53 months (IQR 21–107.5) for the patients without obesity group. There were no significant differences between the groups in five-year PFS (59.9% vs 70.6%, p = 0.135) or OS (68.3% vs 69.3%, p = 0.923). After adjusting for confounders (comorbidities, cancer stage, histopathology, intra- and postoperative complications, and total chemotherapy courses), patients with obesity were not a significant factor for five-year OS or PFS. The adjusted hazard ratio (HR) were 1.074 (95% CI 0.677–1.704, p = 0.762) for OS and 1.430 (95% CI 0.894–2.289, p = 0.136) for PFS (Fig. 1 and 2).

Table 3. Chemotherapy outcomes following epithelial ovarian cancer surgery of 426 patients.

	Total	Patients without obesity (n = 333)	Patients with obesity (n = 93)	p value
Total chemotherapy cycles	6 (6–14.5)	6 (6-15)	6 (6–14)	0.598
Number of patients needing neoadjuvant chemotherapy	51 (12%)	44 (13.2%)	7 (7.5%)	0.135
Side effects				
- Neutropenia	189 (44.5%)	161 (48.5%)	28 (30.1%)	0.002
- Thrombocytopenia	61 (14.4%)	52 (15.7%)	9 (9.7%)	0.146
- Anemia	126 (29.6%)	105 (31.6%)	21 (22.6%)	0.091
- Liver toxicity	33 (7.8%)	28 (8.4%)	5 (5.4%)	0.330
- Neuropathy	320 (75.3%)	248 (74.7%)	72 (77.4%)	0.591
Modification of treatment				
- Delay in administration	212 (49.9%)	176 (53.0%)	36 (38.7%)	0.015
- Dose reduction	35 (8.2%)	28 (8.4%)	7 (7.5%)	0.779
- Discontinuation of therapy	15 (3.5%)	14 (4.2%)	1 (1.1%)	0.208

Data presented as median (interquartile range) or n (%)

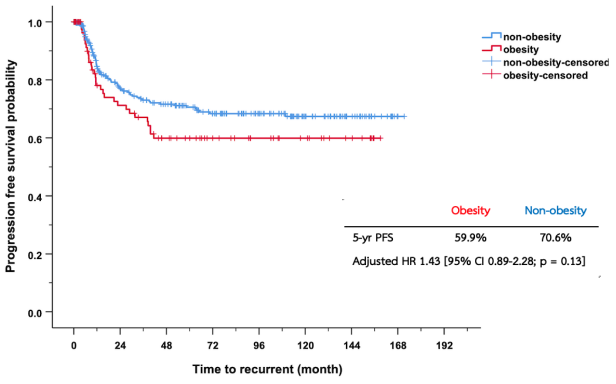

Fig. 1. Kaplan–Meier survival curve demonstrating the progression free survival of patients in both obesity and non-obesity groups.

PFS: progression-free survival, HR: hazard ratio, CI: confidence interval

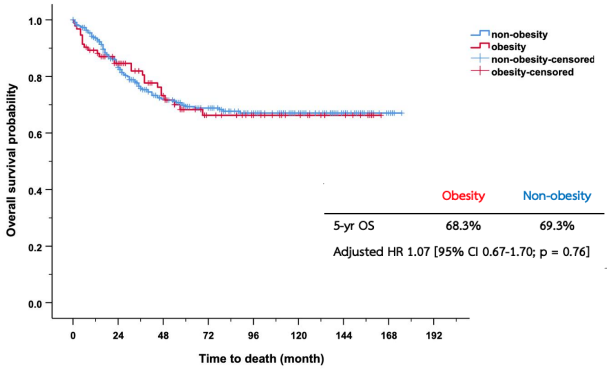

Fig. 2. Kaplan–Meier survival curve demonstrating the overall survival of patients in both obesity and non-obesity groups.

OS: overall survival, HR: hazard ratio, CI: confidence interval

Discussion

The global increase in women with obesity, often referred to as a worldwide epidemic, is mirrored in our study's findings, where 21.9% of patients with ovarian cancer were with obesity. This prevalence was consistent with recent Thai data reporting similar obesity trends among gynecologic cancer patients[18]. The unique challenges presented by individuals with obesity in oncological surgeries, such as increased subcutaneous fat and a thicker adipose layer, can complicate procedures by hindering visibility and access and elevating comorbidity risks.

Hughes et al's systematic review highlighted that 60% of studies reported prolonged operation times, while 35.8% of studies reported an increase in morbidity among patients with obesity who underwent major abdominal cancer surgeries[19]. Similarly, Lv and Wu's 2019 study involving 326 patients with ovarian cancer showed that those in the patients with obesity group underwent longer surgeries, had more blood loss, had longer hospital stays, and had a 50% rate of postoperative complications[20].

In contrast, our study revealed no significant differences in intraoperative outcomes, such as surgical duration, blood loss, lymph node retrieval, or optimal debulking rates, between two groups. However, women with obesity were significantly associated with increased postoperative complications, specifically, wound problems and venous thromboembolism. These findings were in line with the findings of the 2022 meta-analysis by Cai et al, which reported a heightened risk of wound complications in individuals with obesity[21]. Our findings were also consistent with Xu et al's review, which revealed an increased occurrence of postoperative venous thromboembolism in patients with epithelial ovarian cancer and a BMI exceeding 30 kg/m^2 [22].

Postoperative wound complications in patients with obesity may be attributed to the distinct characteristics of adipose tissue. In individuals with obesity, the expansion of adipose tissue is not accompanied by a proportional increase in capillary density, resulting in larger but less efficient blood vessels. This leads to reduced tissue perfusion and a consequent predisposition to hypoxic conditions. Surgical procedures can further exacerbate hypoxia, which negatively impacts the healing process. Moreover, women with obesity-associated comorbidities, such as diabetes, elevate the risk of postoperative infections, further impeding wound healing[23, 24].

Several factors influence the risk of venous thromboembolism in patients with obesity postoperatively. These include increased levels of fibrinogen and certain clotting factors, the presence of systemic inflammation, and elevated intra-abdominal pressure that impairs venous return from the lower limbs[25]. Venous thromboembolism is a major cause of mortality in cancer patients and adversely affects patient prognosis. To mitigate this risk, the American College of Obstetricians and Gynecologists advocate for the routine evaluation of venous thromboembolism risk using the Caprini risk assessment model. The institution also recommends implementing prophylactic strategies tailored to each patient's risk level during gynecologic surgery[26].

The survival outcomes of women with obesity undergoing chemotherapy treatment may be affected by the practice of dose capping. This approach uses ideal or adjusted body weight instead of actual body weight for chemotherapy dose calculations in patients with a BMI of over 25 kg/m^2. This strategy is adopted to prevent the potential toxicities associated with fully dosing. At our center, chemotherapy doses for patients with obesity were calculated using adjusted body weight, which might result in suboptimal dosing. However, our study revealed no significant differences in five-year OS or PFS between the groups. Notably, the women with obesity group experienced significantly fewer incidences of delayed chemotherapy administration and neutropenia. These observations support prior research indicating that dosing chemotherapy based on actual body weight does not significantly increase side effects in patients with obesity, particularly in cases where the goal of treatment is cure[27, 28].

The well-established relationship between optimal cytoreductive surgery and improved survival in patients with ovarian cancer is widely recognized. However, achieving this goal in patients with obesity can pose challenges. Despite these potential challenges, recent systematic reviews have shown no significant difference in optimal debulking surgery rates between patients with or without obesity, even among those classified as patients with class III obesity (BMI ≥ 40 kg/m^2)[21, 29, 30]. These findings suggest that patients with obesity may not significantly impact the ability to perform optimal surgery. In line with these findings, our study revealed no significant differences in the optimal debulking rate or five-year OS or PFS between groups. Furthermore, after adjusting for confounders, patients with obesity did not emerge as a negative prognostic factor for five-year OS (aHR 1.074, 95% CI 0.677–1.704; p = 0.762) or PFS (aHR 1.430, 95% CI 0.894–2.289; p = 0.136). Our results were consistent with previously reported data showing no link between women with obesity and survival in patients with ovarian cancer[10, 11, 14, 31, 32].

The strengths of this study included the large sample size of patients with epithelial ovarian cancer and the long-term follow-up period. However, this study had several limitations that should be acknowledged. First, its retrospective single-institution design introduced the possibility of selection bias and limits the generalizability of the findings to broader populations. Second, missing or incomplete data may have influenced the accuracy of certain clinical variables. Third, the classification of patients into BMI categories at the time of diagnosis may not fully reflect lifetime obesity exposure, weight changes during treatment, or body composition differences such as sarcopenic obesity, which could also impact outcomes.

Additionally, variations in chemotherapy regimens were not accounted for, which may impact the consistency of the cohort and influence chemotherapy-related adverse effects and survival outcomes. Finally, this cohort reflects treatment practices over the past decade; thus, the introduction of novel therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, and advances in minimally invasive or enhanced recovery surgery may alter survival outcomes in contemporary practice, and the findings may not fully capture the impact of these newer approaches.

Conclusion

In conclusion, in ovarian cancer patients with obesity, surgical management requires heightened attention to both perioperative complications and comorbidity optimization. Although operation time, blood loss, hospital stay, and optimal debulking rates were comparable to those in non-obese patients, individuals with obesity demonstrated a substantially increased risk of wound complications and venous thromboembolism. These findings underscored the importance of implementing comprehensive perioperative strategies, including meticulous wound care, advanced dressing techniques, glycemic control, and extended venous thromboembolism prophylaxis. Furthermore, the higher prevalence of diabetes mellitus, hypertension, and dyslipidemia in obese patients highlighted the critical role of prehabilitation programs. Multidisciplinary interventions aimed at optimizing cardiometabolic status, improving functional capacity, and stabilizing chronic conditions before surgery may mitigate perioperative risks and enhance overall surgical recovery.

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Author contributions

A.S.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft; I.R.: conceptualization, writing- review & editing; N.J.: conceptualization, writing- review & editing; K.K.: conceptualization, research design, data curation & analysis, investigation, methodology, validation, visualization, writing – review & editing; V.A.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing – original draft, review & editing. All authors read and approval the final manuscript.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

The Effect of Cold Compression on the Surgical Site Post-Subdermal Contraceptive Implant Insertion to Reduce Bruising and Pain among Female Youth in Family Planning: Randomized controlled trial

Rattiya Chuchot, M.N.S*
Netsumol Jatulajanyalate, M.N.S*
Kritsana Poolperm, M.N.S*
Udomrat Termklinchan, B.N.S**
Somsook Santibenchakul, M.D, Ph.D***
Surasak Taneepanichskul, M.D***

** Maternal and Newborn Nursing and Midwifery Department, Faculty of Nursing, Srisavarindhira Thai Red Cross Institute of Nursing, Bangkok, Thailand*
*** Nursing Department, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*
**** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

ABSTRACT

Objectives: To study the effectiveness of cold compression in reducing bruising and pain around the surgical site following subdermal contraceptive implantation among female youth.

Materials and Methods: Sixty participants aged 18–24 years who attended the family planning clinic for contraceptive implant insertion between March and July 2025 were randomly allocated into two groups. The intervention group (n = 30) received cold compression therapy combined with standard care. A cold compress was applied for 5 minutes before starting the procedure and for 20 minutes at 30 minutes, 7 hours and 18 hours after the procedure. Bruising was assessed at 7, 32, 80 and 152 hours post-procedure. The control group (n = 30) received standard nursing care. Pain was assessed using the visual analog scale (VAS) at 30 minutes, 60 minutes, 8 hours and 19 hours, with a final assessment at 32 hours, during which no cold compress was applied. Bruising and VAS scores were compared at corresponding time points.

Results: The mean size of bruising in the intervention group was significantly smaller than that in the control group at all assessed time points: 7, 32, 80, and 152 hours post-procedure ($p = 0.002$, < 0.001, < 0.001, and < 0.001, respectively). With comparable initial mean VAS scores, the intervention group also reported significantly lower pain levels than the control group post-procedure at 30 minutes, 60 minutes, 8 hours, and 19 hours ($p = 0.039$, < 0.001, 0.01, and < 0.001, respectively). However, no significant difference in pain levels was observed between the groups at 32 hours post-procedure, a time point when the intervention group did not receive cold compression.

Conclusion: This study demonstrated that cold compression for 5 minutes before inserting a

subdermal implant and for 20 minutes three times within 24 hours was more effective in reducing bruising and pain than standard care. No adverse events were reported.

Keywords: contraceptive implantation, female youth, cold compression, bruising, pain, family planning

Correspondence to: *Netsumol Jatulajanyalate, M.N.S, Maternal and Newborn Nursing and Midwifery Department, Faculty of Nursing, Srisavarindhira Thai Red Cross Institute of Nursing, Bangkok, Thailand. E-mail: netsumol.j@stin.ac.th*

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ผลของการประคบเย็นต่อการลดรอยช้ำและความปวดบริเวณแผลหัตถการยาฝังคุมกำเนิดของผู้รับบริการเยาวชนหญิง คลินิกวางแผนครอบครัว: การศึกษาแบบสุ่มมีกลุ่มเปรียบเทียบ

รัตติยา ชูโชติ, เนตรสุมล จตุรจรรยาเลิศ, กฤษณา พูลเพิ่ม, อุดมรัตน์ เติมกลิ่นจันทร์, สมสุข สันติเบ็ญจกุล, สุรศักดิ์ ฐานีพานิชสกุล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลของการประคบเย็นต่อการลดรอยช้ำและบรรเทาความปวดบริเวณแผลหัตถการยาฝังคุมกำเนิด ของผู้รับบริการเยาวชนหญิง*

วัสดุและวิธีการ: *อาสาสมัครเยาวชนหญิง อายุ 18 – 24 ปี จำนวน 60 ราย ที่มารับบริการทำหัตถการยาฝังคุมกำเนิด คลินิกวางแผนครอบครัว ระหว่างเดือนมีนาคม – กรกฎาคม พ.ศ. 2568 สุ่มเข้ากลุ่มทดลอง 30 ราย ได้รับการประคบเย็นนาน 5 นาที ก่อนเริ่มทำหัตถการ และประคบเย็นนานครั้งละ 20 นาที 3 ครั้ง ที่เวลา 30 นาที 7 ชั่วโมง และ 18 ชั่วโมงหลังทำหัตถการ ประเมินรอยช้ำ ที่เวลา 7, 32, 80 และ 152 ชั่วโมงหลังหัตถการ ประเมินความปวดหลังการประคบเย็นแต่ละครั้งด้วย visual analog scale ที่เวลา 30 นาที 60 นาที และ 8, 19 ชั่วโมงหลังทำหัตถการ และประเมินคะแนนปวดครั้งสุดท้ายที่เวลา 32 ชั่วโมงซึ่งเป็นช่วงเวลาที่ไม่มีการประคบเย็น และกลุ่มควบคุม 30 ราย ได้รับการพยาบาลตามปกติ เปรียบเทียบรอยช้ำและความปวดที่เวลาเดียวกันในแต่ละครั้ง*

ผลการศึกษา: *ขนาดรอยช้ำในกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติทุกจุดเวลา ที่ 7, 32, 80 และ 152 ชั่วโมงหลังหัตถการตามลำดับ ($p = 0.002, <0.001, <0.001, <0.001$) และกลุ่มทดลองมีคะแนนความปวดน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ที่เวลา 30 นาที 60 นาที 8 และ 19 ชั่วโมง หลังทำหัตถการ ($p = 0.039, < 0.001, 0.01$ และ < 0.001) ตามลำดับ ทั้งนี้ไม่พบความแตกต่างที่เวลา 32 ชั่วโมง ซึ่งเป็นช่วงเวลาที่กลุ่มทดลองไม่ได้ประคบเย็น*

สรุป: *การประคบเย็นช่วยลดรอยช้ำและบรรเทาความปวดบริเวณแผลหัตถการยาฝังคุมกำเนิดได้เมื่อเปรียบเทียบกับกลุ่ม*

ควบคุม และไม่พบเหตุการณ์ไม่พึงประสงค์จากการประคบเย็น

***คำสำคัญ**: ยาฝังคุมกำเนิด, เยาวชนหญิง, การประคบเย็น, รอยฟกช้ำ, ความปวด, การวางแผนครอบครัว*

Introduction

Bruising and pain are common adverse events following contraceptive implant insertion. Contraceptive implants can be classified into two types according to the number of rods and duration of effectiveness: a single-rod implant, which provides protection for up to three years, and a two-rod implant, effective for up to five years. Both types are inserted subdermally under local anesthesia, typically in the inner aspect of the non-dominant arm. Although no official reports in Thailand describe the incidence of bruising after contraceptive implant insertion, informal reports, personal accounts, and widely shared images on social media indicate that post-procedural bruising is common. These images have caused fear and anxiety among some women, deterring them from undergoing the procedure, despite its high efficacy and recommendation, particularly among adolescents[1, 2, 3].

Post-insertion bruising and ecchymosis, and pain are also common after various surgical and dermatologic procedures. These physical effects may contribute to significant psychological distress in patients[4]. The cause of bruising and pain after the contraceptive implant procedure related to the main contributing factor was the injury from the trocar or applicator used during the procedure, and foreign body reaction leading to acute inflammatory responses[5, 6]. Patients should be systematically assessed to identify any underlying bleeding disorders and evaluate their risk of future bleeding before implant insertion[7].

The clinical care team in the Family Planning Clinic, King Chulalongkorn Memorial Hospital (KCMH), has recognized the critical importance of continuous quality improvement (CQI) to address complications associated with contraceptive implant procedures. Consequently, a comprehensive care protocol was developed to ensure continuity and consistency of care across all stages—pre-, intra-, and post-procedural. This protocol includes detailed wound care instructions, appropriate application of elastic compression bandages, and structured post-discharge follow-up support. To enhance patient self-care and accessibility, communication platforms such as the Line application and institutional telephone services were implemented, allowing timely advice and guidance during recovery. These measures collectively contribute to the overall enhancement of care quality and promote patient engagement in self-management. Despite these efforts, managing post-insertion bruising resulting from tissue trauma remains a clinical challenge. Notably, applying cold compresses before and after the procedure has been shown to reduce tissue injury. Studies have found that the use of ice packs or cold gel packs effectively lowers post-operative pain scores, without any associated adverse effects[8, 9].

This non-pharmacological intervention may help to reduce the extent of bruising and alleviate associated pain, thereby offering an effective adjunct to standard care practices. Continuity of patient-specific care across the pre-, intra- and post-operative phases, including post-discharge and follow-up, improves clinical outcomes[10]. These approaches can be combined with cold compresses tailored to wound type and site, ensuring safety, therapeutic effectiveness, cost-efficiency and convenience. A common method employs elastic bandaging with low-cost cold gel packs and has been shown to reduce

postoperative and procedural complications[11,12].

Cold compression is an effective non-pharmacological intervention for managing wound inflammation and localised pain[13, 14], reflecting the nurse's independent professional role. It reduces pain, inflammation and bruising by decreasing nociceptor activity, constricting blood vessels, lowering tissue temperature and relaxing muscles. Cold compression is most effective within the first 24 to 48 hours after an acute injury. Applying it at 10–20 °C for 20 minutes per session[15], with 1–2 hour intervals, reduces acute inflammatory complications[13,16]. Pre-procedural application for about 5 minutes[11,12] and post-procedural application for about 20 minutes can also minimise post-procedural bruising[17]. This study demonstrated that participants who received cold compression with 5-minute application before the procedure and a 20-minute application after the procedure. The post-procedural cold compress was repeated three times at 30 minutes intervals, following the resolution of local anesthetic effects. Additional applications were incorporated into the patients' daily routine, adapted to outpatient lifestyles, at 7 hours (in the evening of the first day) and 19 hours (the following morning) post-insertion, during time periods when participants were typically at home or in a private residence. These applications remained consistent with the principles of cold compression aimed at minimizing post-procedural complications within the first 24 hours.

A review of the literature revealed no specific cold-compression protocol for wounds inflicted during contraceptive implant insertion. We adapted a standard elastic bandage, tailoring it to wound size and adding a compartment for a standard cold gel pack to provide localized compression, reduce bleeding, bruising, pain, and swelling. By integrating this with the standard care protocol for clients undergoing contraceptive implant insertion at the family planning clinic—covering pre-procedure, intra-procedure and post-procedure phases, with follow-up via telephone and LINE application—the approach aligns with clients' developmental stage and sociocultural context, serving as a guideline for nurses to optimise quality-of-care indicators, particularly post-procedural wound complications. To the best of our knowledge, no prior research has addressed this specific intervention.

Based on the aforementioned rationale and conceptual framework, we were motivated to conduct this study, titled 'The effect of cold compression on the surgical site post-subdermal contraceptive implant insertion to reduce bruising and pain among female youth in family planning'. This intervention is expected to serve as an effective strategy for caring for female youth undergoing contraceptive implant insertion, aimed at reducing post-procedural complication rates and potentially promoting implant uptake among youth. Ultimately, it may contribute to reducing the incidence of unintended teenage pregnancies in alignment with national health policy objectives.

The objectives of the present study were 1) to compare the mean bruise size around the surgical site following subdermal contraceptive implant procedures between female youth who received cold compression care and those who received standard care, and 2) to compare the mean visual analog scale (VAS) pain scores at the surgical site following subdermal contraceptive implant procedures between female youth who received cold compression care and those who received standard care.

Materials and Methods

This study is a randomized controlled trial that was conducted in the family planning clinic, outpatient department, King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand. The study protocol was approved by the ethical committee of the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB# 0548/67) and was registered in the Thai Clinical Trials Registry (TCTR20250222007), and obtained permission from the director of KCMH. The researchers collaborate with the head of the family planning clinic to request permission to conduct the study.

The participants in this study were adolescents or young women (aged 18–24 years) who attended

the family planning clinic for the insertion of subdermal contraceptive implants. Eligible women were informed about the study, and written consent was obtained after they were assessed with the pre-procedure standard care. The inclusion criteria were 18–24-year-old female adolescents who were not pregnant, were presenting to the family planning clinic for first-time insertion of subdermal contraceptive implants, had no coagulation disorders, were not on anticoagulants during this period, did not have underlying cold allergies, had no bruising or pain (VAS score = 0/100) around the surgical site, could understand and communicate in Thai, possessed a smartphone or a device for follow-up phone calls and LINE application and had access to a refrigerator or device to maintain cool temperatures. Participants were excluded if they had received preemptive analgesic medications with prolonged efficacy covering the intraoperative and postoperative periods (e.g., paracetamol or ibuprofen), exhibited allergic reactions to materials used for wound dressing or bandaging, or were unable to attend all scheduled visits as required by the study protocol. Participants were withdrawn from the study if they became pregnant during the study, had a body temperature greater than 37.5°C, developed complications intraoperatively or postoperatively, underwent an implant procedure lasting more than 5 minutes, used long-acting analgesics whose effects persisted during pain data collection, or were non-compliant with cold compress application (adherence < 75%).

Participants were allocated to the intervention and control groups using stratified block randomization with a fixed block size of four. Stratification was based on three variables: age (< 20 or ≥ 20 years), education level (< Bachelor or ≥ Bachelor), and type of contraceptive implant (1-rod or 2-rod), resulting in eight strata. In some strata, only one level of certain variables was present; for example, in the stratum of participants aged < 20 years, no individuals had an education level ≥ Bachelor. For strata with fewer than four participants, simple randomization was applied instead of block randomization.

The control group consisted of participants who received standard nursing care according to the clinical practice guidelines for the management and care of clients receiving contraceptive implant procedures in family planning clinics. This guideline was developed based on the concept of the Service Procedures for Family Planning Clinics[7], integrated with the Standards for Outpatient Nursing Services[18]. This care is provided in three phases: the pre-procedural phase, the intra-procedural phase and the post-procedural phase. The standard care encompasses pre-insertion health assessment and client preparation at the pre-procedure phase. Intra-procedural care involves providing clients with standardised care and support, including the administration of local anaesthesia (1% lidocaine). The insertion site is covered with steri-strips tape, a waterproof film dressing, followed by cold compression or support using an elastic bandage. Standardised post-procedural care includes monitoring and assessing clinical signs and symptoms for a minimum of 30 minutes, followed by patient education on post-procedure self-care, insertion site management demonstration and instruction on the appropriate use of elastic bandages, including the need to keep the elastic pressure bandage dry for 3 days and avoid using the arm for strenuous activities for at least 7 days. After receiving post-procedural care instructions from the nurse provider, the researcher provided guidance and demonstrated to the participants how to use the VAS, to choose the level between 0 (no pain) to 100 (the worst pain) and how to use the standard scale L-shape ruler to measure bruising and photograph the bruise[19]. Pain intensity levels around the surgical site were assessed twice during the hospital stay: once at 30 minutes post-procedure (baseline) and again at 60 minutes post-procedure. Following discharge, pain was assessed at 8, 19 and 32 hours post-procedure. Bruising was measured and photographed at 7, 32 and 80 hours post-procedure (i.e. the evenings of postoperative days 0, 1 and 3) and again at 152 hours post-procedure (evening of day 6). Participants were instructed to record their

data in the form provided. The researcher provided ongoing follow-up care via phone calls and the LINE application, collecting data from the complications record form given to the participants in the control group until the target sample size of 30 participants was reached.

The intervention group consists of participants who received the 'guidelines for cold compress application at the insertion site of contraceptive implant procedures' in addition to the clinical practice guidelines for the management and care of clients receiving contraceptive implant procedures in family planning clinics. The researcher provided care according to the cold compress protocol for post-contraceptive implant insertion site care. This guideline was developed based on the concept of cryotherapy and literature reviews[11, 14, 20-22]. Cold compression was applied using a standard cold gel pack measuring 7 centimetres in width and 10 centimetres in length, with the surface temperature of the fabric wrapped around the gel pack monitored to ensure it remained within the target range of 10 to 15 degrees Celsius. A standard elastic bandage measuring 11 centimetres in width and 50 centimetres in length provided an optimal fit for the contraceptive implant insertion site. The protocol involves three phases: (1) Pre-procedure: applying a cold compression for 5 minutes before starting the procedure; (2) Intra-procedure: providing standard care; (3) Post-procedure: assessing pain levels 30 minutes after the procedure (once the effect of the local anaesthetic had worn off), followed by a 20-minute cold compression application. Afterwards, pain scores were reassessed 60 minutes after the procedure using VAS. After discharge, participants were instructed to continue applying the cold compress for 20 minutes at 7 (evening of day 0) and 18 (morning of day 1) hours post-procedure. Bruising was photographed at 7, 32 and 80 hours post-procedure (i.e. the evening of days 0, 1 and 3) and again at 152 hours post-procedure (evening of day 6). Pain VAS scores were assessed at specific time points. During the observational phase, the VAS scores were taken post-procedure at 30 (baseline) and 60 minutes post-procedure, and then again at 8 and 19 hours after discharge. A final pain assessment was conducted at 32 hours (evening of postoperative day 1) post-procedure, during which no cold compression was applied. Data were recorded in a form, and the researcher provided ongoing follow-up care via phone calls and the LINE application, collecting data from the complications record form given to the participants in the intervention group until the target sample size of 30 participants was reached.

Evaluation of the intervention involved assessing the VAS scores at 30 minutes, 60 minutes, 8 hours, 19 hours and 32 hours post-procedure, as well as the size of the bruise at 7, 32, 80 and 152 hours post-procedure. Bruise dimensions were assessed using a standardised L-shaped measuring ruler. The mean pain scores (VAS) and the mean size of the bruise at the site of insertion were compared between the two groups at each time point.

Cold compress care and the evaluation of pain and bruising at designated time points were conducted in accordance with the clinical care guidelines for patients undergoing contraceptive implant procedures at the family planning clinic and were compatible with the participants' routine daily activities. This was consistent with the recommended cold compress application protocol during the first 24 hours following contraceptive implant insertion.

The sample size in this study was calculated using the G Power program, version 3.1.9.7[23]. Due to limitations in previous studies similar to this one, the sample size calculation was referenced for this study with a 5% type I error, 90% test power and a medium effect size of 0.25[24]. The final sample size reached was 60, with 30 in each group; blocks of four randomisations were used to allocating participants to the groups. Thirty participants were randomised to the control group, where they received standard nursing care, and 30 were randomised to the study group, which received the standard nursing care combined with cold compression care before and after the procedure.

Statistical analysis was performed using SPSS Version 23 (SPSS Inc., Chicago,IL. USA). Descriptive statistics such as frequency distributions, numbers, percentages, means and standard deviations were used to describe participants' characteristics. The mean bruise size and mean VAS scores of participants in the intervention and control groups were analysed using generalized estimating equations (GEEs), with statistical significance set at 0.05.

This study was conducted after consulting an independent biostatistician from the Biostatistics Excellence Center, Faculty of Medicine, Chulalongkorn University. This biostatistician provided short-term guidance regarding study design, sample size and statistical methods.

Results

Fig. 1 is a flowchart describing the participant recruitment process, randomization, intervention and outcome ascertainment in this two-arm parallel group randomized controlled trial. A total of 60 participants presenting at the family planning clinic during the study period were selected, with 30 in each group. There were no participants lost to follow-up in either group. The baseline demographic and clinical characteristics of the study participants (Table 1) indicated that the randomisation process successfully generated highly comparable control and intervention groups. The mean age of participants in both groups was 21.0 years; 70% of participants had a secondary level of education, and half of the participants used the same type of contraceptive implant. There was all presented no difference in both groups.

Table 2 shows results of the chi-square analysis, that the rate of the non-bruising (bruise size = 0 cm^2) incident in the intervention group was significantly higher than that in the control group across all evaluation time points, including at 7 ($p < 0.001$), 32 ($p < 0.001$), 80 ($p < 0.001$) and 152 ($p = 0.001$) hours post-procedure, respectively.

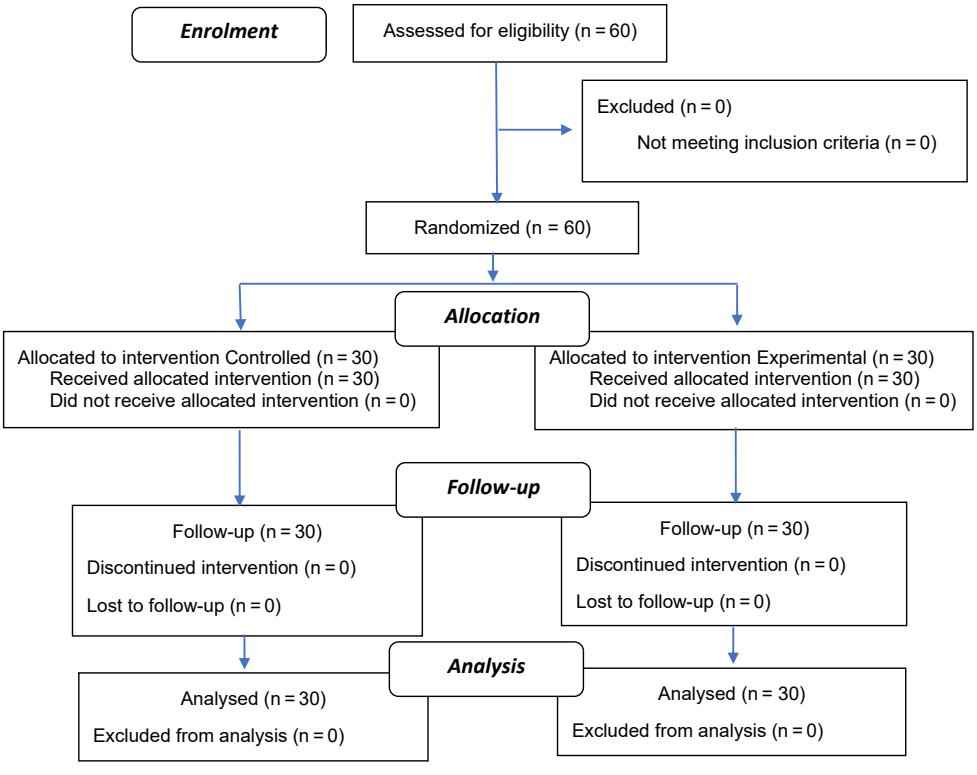

Fig. 1. The consort flowchart of randomization..

Table 1. The Baseline characteristics of the study participants.

Characteristics	Control (n = 30)	Intervention (n = 30)	Total (n = 60)
Age (years), mean ± SD	21.0 ± 2.0	21.0 ± 2.0	21.0 ± 2.0
Education level, n (%)			
Secondary	21 (70.0)	21 (70.0)	42 (70.0)
≥ Bachelor	9 (30.0)	9 (30.0)	18 (30.0)
No Underlying disease, n (%)	30 (100.0)	30 (100.0)	60 (100.0)
Type of contraceptive implant, n (%)			
1 rod	15 (50.0)	15 (50.0)	30 (50.0)
2 rods	15 (50.0)	15 (50.0)	30 (50.0)
History of contraceptive use, n (%)			
Never used	2 (6.7)	3 (10.0)	5 (8.3)
Previously used	28 (93.3)	27 (90.0)	55 (91.7)
Number of methods, n (%)			
1 method	11 (36.7)	15 (50.0)	26 (43.3)
2 methods	13 (43.3)	11 (36.7)	24 (40.0)
3 methods	6 (20.0)	4 (13.3)	10 (16.7)
Methods previously used, n (%)			
Combine oral contraceptives (COCs)	11 (36.7)	8 (26.7)	19 (31.7)
Injectable contraceptives	2 (6.7)	7 (23.3)	9 (15.0)
Emergency contraceptive pills (ECPs)	14 (46.7)	9 (30.0)	23 (38.3)
Condom	26 (86.7)	22 (73.3)	48 (80.0)
Intrauterine devices (IUD)	0 (0.0)	1 (3.3)	1 (1.7)

SD: standard deviation

Table 2. Comparison of the non-bruising (bruise size = 0 cm^2) incidence in the participants between groups at the time point post procedure.

Time point post procedure	Control (n = 30)	Intervention (n = 30)	X^2	dt	p value
7 hours	4 (13.33%)	27 (90%)	35.31	1	< 0.001
32 hours	1 (3.33%)	23 (76.67%)	33.61	1	< 0.001
80 hours	0 (0%)	13 (43.33)	16.60	1	< 0.001
152 hours	0 (0%)	10 (33.33)	12.00	1	0.001

Table 3 shows that according to the GEE analysis, the intervention group demonstrated significant efficacy of cold compression in preventing and reducing the size of bruises, with statistically significant differences observed at all assessed time points, including at 7 hours (mean difference = 2.97, $p < 0.002$), 32 hours (mean difference = 4.10, $p < 0.001$), 80 hours (mean difference = 9.64, $p < 0.001$) and 152 hours (mean difference = 12.52, $p < 0.001$) post procedure, respectively.

Table 3. Comparison of mean size of bruise (cm^2) between groups at the time point post procedure.

Time points post procedure	Control (n = 30) mean (SE)	Study (n = 30) mean (SE)	mean difference (95% CI)	p value
7 hours	3.00 (0.98)	0.03 (0.02)	2.97 (1.05, 4.89)	0.002
32 hours	4.19 (0.99)	0.09 (0.04)	4.10 (2.16, 6.03)	< 0.001
80 hours	10.00 (1.29)	0.36 (0.08)	9.64 (7.10, 12.18)	< 0.001
152 hours	12.91 (1.72)	0.39 (0.09)	12.52 (9.14, 15.90)	< 0.001

SE: standard error, CI: confidence interval

Table 4 shows results of the GEE analysis, demonstrating that the intervention group receiving cold compression therapy reported significantly lower pain scores compared to the control group at the 30-minute (mean difference = 2.37, p = 0.039), 1-hour (mean difference = 10.83, p < 0.001), 8-hour (mean difference = 10.17, p = 0.01) and 19-hour (mean difference = 9.99, p < 0.001) time point. There was no statistically significant difference in pain scores between the groups at 32 hours (mean difference = 6.57, p = 0.103).

Table 4. Comparison of pain visual analog scale (VAS) scores between groups at the time point post procedure.

Time point post procedure	Control (n = 30) mean (SE)	Intervention (n = 30) mean (SE)	mean difference (95% CI)	p value
30 minutes	4.43 (0.83)	*2.07 (0.79)	2.37 (0.12, 4.62)	0.039
1 hours	10.83 (1.00)	**0.00 (0.00)	10.83 (8.87, 12.80)	< 0.001
8 hours	19.53 (3.53)	**9.37 (1.74)	10.17 (2.46, 17.87)	0.01
19 hours	13.80 (2.28)	**3.81 (1.31)	9.99 (4.48, 15.14)	< 0.001
32 hours	15.93 (3.17)	***9.37 (2.47)	6.57 (-1.32, 14.45)	0.103

SE: standard error, CI: confidence interval, VAS: visual analogue scale (0 = no pain, 100 = the worst pain)

* mean VAS after the procedure and received a cold compress for 5 minutes before starting the procedure

** mean of VAS after receiving a 20-minute cold compress

Discussion

Contraceptive implants, classified as long-acting reversible contraceptives (LARCs), are widely recognized for their high safety and effectiveness and have been promoted as a key strategy to prevent unintended pregnancy among female youth[2, 3]. Nevertheless, concerns remain regarding side effects, such as menstrual irregularities, dizziness, and mood changes, as well as procedural complications, including pain and bruising. Although complications at the implant insertion site are typically minor and self-limiting, they can influence user satisfaction, acceptance, and continuation[25]. Among adolescents, concerns regarding bruising and pain have been associated with reluctance to initiate use. Bruising may adversely affect body image, further impacting the overall user experience[26]. In addition, post-procedural pain following implant insertion may increase patient anxiety, which can in turn amplify pain perception[27], resulting in physical and emotional discomfort.

Therefore, healthcare providers should develop appropriate measures to prevent or alleviate local complications. Cold compression has been recognised as an effective method to relieve pain and reduce bruising following implant insertion. Pharmacokinetic

evidence indicates that contraceptive implants release hormones consistently and continuously, independent of temperature or local environmental conditions at the insertion site[28]. Furthermore, cold compression is a low-cost intervention that can be easily applied in clinical practice to mitigate adverse local symptoms after implant insertion.

This study demonstrated that participants who received cold compression with 5-minute application before the procedure and a 20-minute application after the procedure. The post-procedural cold compress was repeated three times at 30 minutes, 7 hours, and 19 hours following the procedure had a lower incidence of bruising compared with the control group. Specifically, the proportion of participants with no bruising (bruise site = 0 cm^2) was significantly higher in the intervention group, and bruise sizes at 7, 32, 80 and 152 hours were significantly smaller in the intervention group than in the control group. These effects are attributed to local cooling at the implant site, which lowers skin and subcutaneous tissue temperature, inducing vasoconstriction as an initial response. Subsequently, the sympathetic nervous system reflexively stimulates α-receptors, causing further vasoconstriction, reduced blood flow and decreased delivery of oxygen and nutrients, thereby slowing cellular metabolism in the area. Reduced local circulation is a key mechanism by which cold application decreases swelling and bruising[29].

These findings were consistent with those of previous research on the use of cold compresses in minor procedures. Participants receiving standard care developed significantly larger bruises at 48 and 72 hours following subcutaneous anticoagulant injection compared with those who received a cold compress either 5 minutes before or after the injection[30]. Cold compress applied for 5 minutes prior to the injection also significantly reduced the incidence of bruising[20]. Furthermore, meta-analyses have confirmed that cold compress application for 2–5 minutes, either before or after subcutaneous injection, effectively reduces bruising without serious adverse effects[21, 31].

However, evidence on bruise management following contraceptive implant insertion remains limited. Accordingly, this study adapted cold compression protocols from patients receiving subcutaneous heparin injections, in which cold compression was applied for 5 minutes before the procedure[11, 12] and for 20 minutes afterward[17]. The extended duration in our protocol aimed to further reduce local inflammation and bruising, as contraceptive implant insertion causes slightly more tissue trauma than a standard subcutaneous injection. In addition, because the implanted device acts as a foreign object that may trigger an inflammatory response, two additional post-procedural cold compression sessions were applied. General recommendations suggest 2–3 cold compression sessions per day, 20 minutes each, with gel packs at a surface temperature of 10–20 °C for post-injury or post-procedural care[16]. In this study, the protocol was adapted to be practical and compatible with participants' daily routines. Similar postoperative studies in cesarean delivery applied a single 20-minute cold gel pack session 2 hours after surgery without changing the pack, and no adverse events were reported[8].

This study found that participants who received cold compresses according to the cold compress protocol for post-contraceptive implant insertion site care reported significantly lower pain levels than those in the control group at 30 minutes and at 1, 8 and 19 hours after contraceptive implant insertion, with VAS scores evaluated after the administration of the cold compress. This result can be explained by the gate control theory of pain proposed in 1965[5], which posits that pain signals are transmitted through small-diameter nerve fibres (A-delta and C fibres) to the dorsal horn of the spinal cord. At this site, substantia gelatinosa (SG) cells modulate a 'gate' that regulates the transmission of pain impulses to transmission cells (T-cells) and subsequently to the brain. Cold stimulation activates large-diameter fibres (A-beta and A-alpha), which stimulate SG cells to close the gate, thereby inhibiting pain transmission. In addition, cold compression reduces local blood flow, slows tissue

metabolism, decreases muscle tension and may activate central opioid receptors, all of which result in reduced pain perception. These findings are consistent with those of prior studies. Karadağ et al reported that participants who received cold compresses experienced significantly lesser pain than those who received manual pressure following subcutaneous anticoagulant injection[22]. Similarly, a systematic review demonstrated that cold application before or after subcutaneous injection significantly reduces pain intensity[12]. Moreover, Wongcharoen and Inta found that combining cold gel packs with standard care resulted in lower pain scores during and after needle insertion compared to standard care alone[32].

However, by 32 hours post-procedure during which no applied cold compression, pain scores were not significantly different between the intervention and control groups. It may be explained by the natural resolution of acute tissue inflammation and the fact that cold compresses were applied only during the first 24 hours after the procedure. Similar patterns have been observed in other surgical settings, such as Caesarean delivery, where cold gel packs effectively reduced early postoperative pain but had minimal effect beyond 24 hours[8]. These results suggest that cold compresses provide short-term analgesic benefits, highlighting the importance of early application after the procedure, while additional pain management strategies may be necessary for later time points.

We acknowledge that the bruise size and VAS were low in both groups, which likely reflects the effectiveness of the standard nursing care provided to the control group, including careful pre-, intra-, and post-procedural monitoring, VAS assessment, bruising measurement, and ongoing follow-up, similar to the intervention group. Despite the overall low scores, statistical analysis showed a significant reduction in pain and bruising in the intervention group, indicating the additional benefit of the cold compress protocol beyond standard care.

In this study, participants received care following the management and care of clients receiving contraceptive implant procedures in family planning clinics guidelines, which encompass pre-, intra- and post-procedural support, side effect monitoring and self-care instruction provision via the LINE official account after discharge. Continuous follow-up through youth-appropriate communication channels has been shown to enhance post-insertion self-care, reduce anxiety, increase satisfaction and allow for safe management of minor adverse events without requiring a return visit[10, 33, 34].

This randomized controlled trial demonstrated notable strengths, including the absence of adverse events and participant dropout, underscoring the feasibility and safety of the intervention. Nonetheless, several limitations should be considered. The unblinded design may have introduced bias in participants' reporting of bruising and pain, and the requirement for repeated cold compression applications could have influenced adherence to the intervention protocol. While bruising incidence and size were systematically monitored, the evaluation of color changes over time was limited, as participant-submitted smartphone images via the LINE application introduced variability in image quality and color consistency, thereby reducing the precision of outcome assessment. Future studies employing blinded designs, standardized image capture methods, and streamlined intervention protocols are warranted to validate these findings and enhance their generalizability.

Conclusion

Application of a cold compress at the contraceptive implant insertion site, involving a 5-minute pre-procedure and 20-minute post-procedure application, with additional post-procedural compresses at 30 minutes, 7 hours, and 19 hours, was an effective, non-technology innovation for reducing pain and bruising. In this study, participants who received care according to the cold compress protocol reported significantly lower pain levels and smaller bruises compared with the control group. No adverse events were reported.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Adherence to Venous Thromboembolism Prophylaxis in High-Risk Gynecologic Cancer Patients during the Enhanced Recovery after Surgery Era

Sirada Tachatiemchan, M.D.*,
Atcharaporn Prathumsuwan, M.N.S.**,
Dittakarn Boriboonhirunsarn, M.D.*,
Tarinee Rungjirajittranon, M.D.***,
Vuthinun Achariyapota, M.D.*,
Atthapon Jaishuen, M.D.*,
Vitcha Poonyakanok, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University*
*** Obstetrics and Gynaecological Nursing Division, Department of Nursing Siriraj Hospital*
**** Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.*

ABSTRACT

Objectives: Venous thromboembolism (VTE) is a common complication in patients with gynecologic cancer, reducing survival and increasing the financial burden. This study aimed to assess the adherence to VTE prophylaxis and factors that influence physician decisions.

Materials and Methods: This descriptive cross-sectional study was conducted in the Department of Obstetrics and Gynecology, Siriraj Hospital, Thailand. We included patients with gynecologic malignancies undergoing abdominopelvic surgery who were at high risk for VTE (Caprini score ≥ 5). Patient demographics, clinical profiles, and the adherence of the physician to the thromboprophylaxis protocols were evaluated.

Results: From October 2023 to October 2024, 231 patients met the inclusion criteria. The median age was 59 years (interquartile range (IQR) 50–66) and the median body mass index was 24.4 kg/m² (IQR 21.1–28). Most patients (83.2%) had Caprini scores of 5 or 6. 219 (96.5%) patients received mechanical and/or pharmacological prophylaxis. However, only 50 patients (22%) received prophylaxis in accordance with the guidelines. The surgical route was the only factor significantly associated with guideline adherence.

Conclusion: The adherence rate to VTE prophylaxis in perioperative gynecologic malignancy patients was low (22%). Further research is needed to understand barriers to adherence and the clinical consequences of noncompliance.

Keywords: venous thromboembolism, anticoagulants, female genital neoplasms, guideline adherence.

Correspondence to: *Vitcha Poonyakanok, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. E-mail: vitcha.poo@mahidol.ac.th*

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อัตราการปฏิบัติตามแนวทางป้องกันการเกิดภาวะลิ่มเลือดอุดตันหลอดเลือดดำในผู้ป่วยมะเร็งนรีเวชที่เข้ารับการผ่าตัดและมีความเสี่ยงต่อการเกิดลิ่มเลือดอุดตันหลอดเลือดดำในช่วงโปรแกรม ERAS

ศิรดา เตชะเทียมจันทร์, อัชราภรณ์ ประทุมสุวรรณ, ธาริณี รุ่งจิรจิตรานนท์, ดิฐกานต์ บริบูรณ์หิรัญสาร, วุฒินันท์ อัจฉริยะโพธา, อรรถพล ใจซื่น, วิชชา ปุณยกนก

บทคัดย่อ

วัตถุประสงค์*: ภาวะลิ่มเลือดอุดตันในหลอดเลือดดำเป็นภาวะแทรกซ้อนที่พบบ่อยในผู้ป่วยมะเร็งนรีเวช ซึ่งส่งผลให้อัตราการรอดชีวิตลดลงและเพิ่มภาระค่าใช้จ่ายทางการแพทย์ งานวิจัยนี้มีวัตถุประสงค์เพื่อประเมินการปฏิบัติตามแนวทางการป้องกัน การเกิดภาวะลิ่มเลือดอุดตันหลอดเลือดดำและปัจจัยที่มีผลต่อการปฏิบัติตามแนวทาง*

วัสดุและวิธีการ*: การศึกษานี้เป็นการศึกษาแบบตัดขวางเชิงพรรณนา ทำการศึกษาในผู้ป่วยที่เป็นมะเร็งนรีเวชและเข้ารับการผ่าตัดในช่องท้องหรืออุ้งเชิงกราน ซึ่งมีความเสี่ยงสูงต่อการเกิดการเกิดภาวะลิ่มเลือดอุดตันหลอดเลือดดำ (คะแนน Caprini ≥ 5) ที่โรงพยาบาลศิริราช ตัวแปรข้อมูลทั่วไป ประวัติทางคลินิก และการปฏิบัติตามแนวทางการให้ยาป้องกันการเกิดลิ่มเลือดอุดตันของแพทย์ ถูกจัดเก็บและนำมาประเมิน*

ผลการศึกษา*: การศึกษานี้รวบรวมข้อมูลระหว่างเดือนตุลาคม พ.ศ. 2566 ถึงตุลาคม พ.ศ. 2567 โดยมีผู้ป่วยจำนวน 231 รายที่เข้าเกณฑ์ อายุมัธยฐานอยู่ที่ 59 ปี (พิสัยระหว่างควอร์ไทล์ 50–66) ค่าดัชนีมวลกายมัธยฐาน 24.4 กก./ม² (พิสัยระหว่างควอร์ไทล์ 21.1–28) ผู้ป่วยส่วนใหญ่ (ร้อยละ 83.2) มีคะแนน Caprini เท่ากับ 5 หรือ 6 มีผู้ป่วย 219 ราย (ร้อยละ 96.5) ได้รับการป้องกันด้วยวิธีกลและ/หรือการใช้ยาต้านการแข็งตัวของเลือด อย่างไรก็ตาม มีผู้ป่วยเพียง 50 ราย (ร้อยละ 22) ที่ได้รับการป้องกันตรงตามแนวทางที่กำหนด ปัจจัยเดียวที่สัมพันธ์อย่างมีนัยสำคัญกับการปฏิบัติตามแนวทางคือช่องทางการผ่าตัด*

สรุป*: อัตราการปฏิบัติตามแนวทางการป้องกันการเกิดภาวะลิ่มเลือดอุดตันหลอดเลือดดำในผู้ป่วยมะเร็งนรีเวชช่วงก่อนและหลังผ่าตัดมีเพียงร้อยละ 22 ควรมีการศึกษาวิจัยเพิ่มเติมเพื่อทำความเข้าใจอุปสรรคที่ทำให้ไม่ปฏิบัติตามแนวทาง และผลลัพธ์ทางคลินิกที่เกิดจากการไม่ปฏิบัติตาม*

คำสำคัญ*: ภาวะลิ่มเลือดอุดตันในหลอดเลือดดำ, ยาต้านการแข็งตัวของเลือด, เนื้องอกในอวัยวะสืบพันธุ์สตรี*

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the leading causes of morbidity and mortality in gynecologic oncology. Patients with malignancies and those undergoing pelvic surgery have an elevated risk of VTE, making gynecological oncology patients a particularly high-risk population[1]. The RISTOS study is a prospective observational study involving more than 2,000 surgical patients; 20% underwent gynecologic procedures with a VTE incidence of 2%. Notably, 40% of the events occurred more than 21 days after surgery[2]. The prognosis of patients who develop malignancy-associated VTE is poorer than that of those who do not, across all gynecological cancer types[3]. For instance, in one large 7-year study of cervical cancer patients, the 5-year survival rate was nearly 80% in those without VTE, compared to just under 40% in those who developed VTE[4].

The randomized controlled trial by Bergqvist et al in 2002 showed that enoxaparin prophylaxis for four weeks after surgery for abdominal or pelvic cancer significantly reduced the rate of VTE compared to a one-week regimen[5]. The guidelines from the American College of Chest Physicians (ACCP) in 2012, the American College of Obstetricians and Gynecologists (ACOG) in 2021, the American Society of Clinical Oncology (ASCO) in 2023, and the European Society for Medical Oncology (ESMO) in 2023 recommend the use of low molecular weight heparin (LMWH) combined with intermittent pneumatic compression, followed by extended LMWH for 4 weeks in patients at high risk for VTE[6-9].

In 2001, the Enhanced Recovery After Surgery (ERAS) Society developed a protocol to improve surgical patient outcomes through a multimodal, multidisciplinary approach, with VTE prophylaxis included as part of the care bundle. ERAS protocols have been shown to reduce the length of hospital stay by 30% to 50%, along with similar reductions in complication rates[10]. Building on this in July 2023, our department launched an ERAS protocol and a local VTE prophylaxis guideline for malignancy patients. Most high-risk patients received mechanical prophylaxis, but the use of pharmacological prophylaxis varied depending on physician preference. Additionally, data from a multinational registry study conducted in Latin America, Africa and the Middle East reported that prescriptions adhered to ACCP guidelines in 73.9% of patients during hospitalization, but only 18.9% after discharge[11]. The primary objective of this study was to evaluate adherence to VTE prophylaxis in high-risk gynecologic cancer patients during the ERAS period. The secondary objective was to identify factors that influence medical decisions about prophylaxis.

Materials and Methods

This was a single-center cross-sectional descriptive study conducted from October 2023 to October 2024 in the Department of Obstetrics and Gynecology of Siriraj Hospital. The study received approval from the Siriraj Institutional Review Board (CoA No. 950/2024). Based on a review of electronic medical records, the study included patients who were preoperatively diagnosed with gynecologic malignancy, admitted for abdominopelvic surgery and identified as a high risk of VTE defined by a Caprini score of 5 or higher. Patients with a prior diagnosis of deep vein thrombosis or pulmonary embolism, those currently using anticoagulant therapy, and those whose tumors were diagnosed as benign after surgery were excluded. The characteristics of the patients including clinical details and operation profiles, and adherence to the prescribed thromboprophylaxis protocols were assessed. Radical surgery was defined as an extensive procedure that carries an increased risk of complications. For example, radical hysterectomy or vulvectomy, lymphadenectomy, peritonectomy, tumor debulking, and bowel or bladder surgery.

On July 1, 2023, the Department of Obstetrics and Gynecology at Siriraj Hospital adopted an ERAS protocol along with a local VTE prophylaxis guideline. As part of the preoperative evaluation, all patients with

gynecologic malignancy were assessed using the Siriraj DVT scoring system to identify those at high risk of asymptomatic DVT[12]. High risk patients underwent a lower extremity Doppler ultrasound. Those diagnosed with DVT received appropriate treatment and their surgery was postponed. On the day of admission before surgery, each patient was evaluated using the Caprini score to determine the appropriate VTE prophylaxis. For high-risk patients with a Caprini score of 5 or higher, a combination of mechanical methods, such as intermittent pneumatic compression and extended duration anticoagulation therapy, was recommended. The choice of prophylaxis was ultimately determined by the surgeon. During the postoperative period, leg circumference was measured daily until discharge. If the circumference difference exceeded 2 cm or if the patient experienced desaturation - both potential signs of VTE - further evaluation with Doppler ultrasound and/or chest CT angiography was performed.

Complete adherence to thromboprophylaxis for high-risk patients was defined according to our local guideline as the combined use of mechanical and pharmacological prophylaxis, with an extended regimen of 28 days post-operation. Partial adherence was defined as the use of mechanical or pharmacological prophylaxis alone, or the incomplete use of either.

The sample size was calculated based on a previous study, which reported a thromboprophylaxis compliance rate of 73%[11] with a 10% margin of error. A total of 231 atients were included in the study, accounting for an anticipated 10% data loss.

Data were analyzed using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, NY). Baseline characteristics and data on prophylaxis use were presented using the median and interquartile range for continuous variables and number and percentage for categorical variables. Factors associated with complete adherence to the VTE prophylaxis protocol were analyzed using the Chi square test or Fisher's exact test. To identify independent predictors of adherence, variables with a p value < 0.1 in the univariate analysis were included in a multivariate analysis using logistic regression. A p value less than 0.05 was considered statistically significant.

Results

Data were retrieved from 231 patients between October 2023 and October 2024. After excluding 4 patients without malignancies, a total of 227 patients remained for analysis The median age was 59 years (interquartile range (IQR) 50-66) and the median body mass index (BMI) was 24.4 kg/m² (IQR 21.1-28). Approximately two-thirds of the patients had at least one chronic illness, primarily hypertension. Additionally, 6.6% of patients were using antiplatelet drugs. The most common primary cancer site was the endometrium (58.6%), followed by the ovary (30.4%) and cervix (10.6%). Half of the patients were at stage 1 of the disease, while 16.7% were at stage 4. The Caprini score was used to evaluate perioperative DVT risk in all patients: 87 (38.3%) had a score of five, 102 (44.9%) had a score of six, 30 (13.2%) had a score of seven, and 8 (3.6%) had a score of eight.

Of the 227 patients included in the analysis, 219 (96.5%) received at least one form of VTE prophylaxis. Combined mechanical and pharmacological prophylaxis was administered to 59.4% of patients, while 38.4% and 5.0% received mechanical or pharmacological prophylaxis alone, respectively. Among the 135 patients who received both mechanical and pharmacological prophylaxis, 80 (59.3%) were prescribed anticoagulants only preoperatively, 50 (37.0%) received extended anticoagulation for 4 weeks, 4 (3.0%) were prescribed anticoagulants for less than four weeks, and 1 (0.7%) received pharmacological prophylaxis solely during hospitalization. Enoxaparin was the exclusive pharmacological agent utilized. Complete adherence to the local guideline, defined as receiving anticoagulants both preoperatively and for 28 days postoperatively, in addition to mechanical prophylaxis, was observed in only 50 patients (22.0%). The baseline characteristics of the patients are summarized in Table 1, and the utilization of prophylaxis among gynecologic cancer patients undergoing surgery is presented in Table 2.

Table 1. Baseline characteristics of patients with gynecological cancer who underwent surgery (n = 227).

Characteristics	n = 227 (%)
Age (years)	
> 60	102 (44.9)
≤ 60	125 (55.1)
BMI (kg/m^2)	
≥ 25	100 (44.1)
< 25	127 (55.9)
History of chronic illness	150 (66.1)
Diabetes mellitus	45 (19.8)
Hypertension	82 (36.1)
Cardiovascular disease	7 (3.1)
Current antiplatelet drug use	15 (6.6)
Primary cancer organ	
Ovary	69 (30.4)
Endometrium	133 (58.6)
Cervix	24 (10.6)
Vulva	1 (0.4)
Stage of the disease	
1	114 (50.2)
2	31 (13.7)
3	44 (19.4)
4	38 (16.7)
Blood loss (ml)	
≤ 500	180 (79.3)
> 500	47 (20.7)
Radicality of surgery	
Yes	193 (85)
No	34 (15)
Residual disease	
Yes	49 (21.6)
No	178 (78.4)
Caprini score	
5	87 (38.3)
6	102 (44.9)
7	30 (13.2)
8	8 (3.6)

* Data are presented as number (%).
BMI: body mass index

Table 2. Usage of prophylaxis in gynecologic cancer patients undergoing surgery (n = 227).

VTE prophylaxis	n = 227 (%)
No VTE prophylaxis	8 (3.5)
Any VTE prophylaxis	219 (96.5)
Type of VTE prophylaxis*	
Mechanical prophylaxis alone	84 (38.4)
Pharmacological prophylaxis alone	5 (2.3)
Mechanical and pharmacological prophylaxis	130 (59.4)
Type of Pharmacological prophylaxis†	
Only pre-operative	80 (59.3)
Only hospitalization	1 (0.7)
Duration of post-operative anticoagulant (weeks)	
< 4 weeks	4 (3)
4 weeks	50 (37)

VTE: venous thromboembolism
* n = 219
† n = 135

The univariate analysis of patient factors associated with complete adherence to the VTE prophylaxis guideline is presented in Table 3. Among the variables analyzed, the only factor that was significantly associated with adherence was the surgical approach. Patients who underwent laparotomy were more likely to receive appropriate prophylaxis compared to those who underwent laparoscopic surgery. Other factors, including age, BMI, presence of chronic illness, primary cancer site, stage of the disease, and Caprini score, were not significantly associated with adherence to the prophylaxis protocol. Notably, factors such as the radical nature of the surgery and intraoperative blood loss were also found to be associated with adherence to the prophylaxis protocol. A multivariate analysis was not conducted because only one factor demonstrated a p value less than 0.1 in the univariate analysis.

Table 3. Factors associated with complete adherence to VTE prophylaxis guidelines.

Factors	VTE adherence to guideline		p value
	Yes (%)	No (%)	
Age (years)			0.144
> 60	27 (54)	75 (42.4)	
≤ 60	23 (46)	102 (57.6)	
BMI (kg/m^2)			0.513
≥ 25	20 (10)	80 (45.2)	
< 25	30 (60)	97 (54.8)	
Chronic illness			0.317
Yes	36 (72)	114 (64.4)	
No	14 (28)	63 (35.6)	
Organ			0.149
Ovary	17 (34)	52 (29.4)	
Cervix	1 (2)	23 (13)	
Endometrium	32 (64)	101 (57.1)	
Vulva	0	1(0.6)	
Stage			0.754
Early stage (1-2)	31 (62)	114 (64.4)	
Advance stage (3-4)	19 (38)	63 (35.6)	
Route of surgery			0.034
Laparotomy	45 (90)	135 (76.3)	
Laparoscopy	5 (10)	42 (23.7)	
Blood loss(ml)			0.497
≤ 500	40 (80)	139 (78.5)	
> 500	10 (20)	38 (21.5)	
Radical surgery			0.504
Yes	44 (88)	149 (84.2)	
No	6 (12)	28 (15.8)	
Caprini score			0.148
5-6	45 (91.8)	144 (81.4)	
More than 6	5 (10.2)	33 (18.6)	

VTE: venous thromboembolism

Discussion

Our study aimed to evaluate the rate of adherence to VTE prophylaxis in the era of ERAS. In Thailand, ERAS has been shown to significantly reduce length of stay and improve recovery in the first 24 hours after surgery[13, 14]. While many professional societies have promoted the implementation of clinical guidelines and the ERAS society has included VTE prophylaxis as part of its recommended care bundle to accelerate patient recovery, we found that adherence remains suboptimal. In our cohort of patients with high-risk gynecologic cancer who underwent surgery, only 22% received VTE prophylaxis in full accordance with the guidelines.

The main reason for incomplete adherence was the failure to provide the full recommended duration of pharmacological prophylaxis with LMWH. VTE occured in approximately 4% of patients undergoing gynecologic cancer surgery, with approximately three-quarters of these events detected more than seven days postoperatively[15]. Based on these findings, a randomized controlled trial conducted in 2002 demonstrated that a four-week course of enoxaparin following abdominal or pelvic cancer surgery significantly reduced the incidence of venographically confirmed thrombosis compared to a one-week regimen, without compromising safety[5]. In our institution, we have implemented a VTE prophylaxis protocol that includes extended medical prophylaxis that aligns with international recommendations. In addition, the Gynecologic Cancer Society of Thailand is developing a new guideline that may have a significant impact on national practice.

Schemeler et al demonstrated that the incidence of VTE within 20 days postoperatively decreased from 2.7% to 0.6% following the implementation of VTE prevention guidelines[16]. Extended duration thromboprophylaxis has also been shown to be cost-effective in abdominal oncologic surgeries. According to Iannuzzi et al (2014), it was the dominant strategy when the probability of VTE exceeded 2.39%, based on a willingness-to-pay threshold of $50,000 per quality-adjusted life year (QALY)[17]. Despite strong evidence supporting extended prophylaxis, adherence to these recommendations remains poor. The compliance rate was only 18.9% for abdominal and pelvic cancer surgeries in Latin America, Africa, and the Middle East[11]. In the U.S. Medicare population consisting of individuals aged 65 and older, as well as younger people with disabilities or end-stage renal disease undergoing major abdominal cancer operations, 8.9% received extended prophylaxis[18]. Our study, which focused specifically on high-risk gynecologic cancer patients, found a compliance rate of 22%.

Currently, there are no data on the incidence of VTE in perioperative gynecologic oncology patients considered to be at high risk of VTE in Thailand. However, two studies conducted in Thailand reported a 7% incidence of DVT among critically ill medical patients[19] and a notably higher 21% incidence of VTE among hospitalized cancer patients with clinically suspected VTE[20]. These findings underscore the need for further research to determine the true incidence of VTE in high-risk perioperative gynecologic oncology patients in Thailand. The incidence in this specific group may differ from that reported in other regions. If this is true, current VTE prophylaxis guidelines may need to be adapted to reflect local epidemiological and clinical characteristics.

Several explanations for the underuse of thromboprophylaxis have been proposed, including the perceived lack of evidence, brief periods of postoperative immobilization, shorter operative times, and notably, the increasing use of minimally invasive (laparoscopic) surgical techniques[21]. While laparoscopic approaches are associated with less blood loss, fewer complications, and faster recovery, the use of the Trendelenburg position and potentially longer operative times may increase the risk of VTE[22]. A study involving 301 patients undergoing laparoscopic surgery for colorectal cancer found that VTE occurred in 11 of 113 patients who received

short-duration prophylaxis, whereas no events occurred among the 112 patients who received extended prophylaxis, supporting the safety and efficacy of prolonged anticoagulation[23]. Currently, international guidelines such as those of the ASCO and the ESMO do not differentiate between surgical modalities when recommending extended VTE prophylaxis after cancer surgery. In our study, however, patients who underwent laparotomy were more likely to receive appropriate thromboprophylaxis compared to those who underwent laparoscopic surgery.

Obesity is a factor that increases postoperative complications, elevates the risk of VTE, and prolongs hospital stay[24, 25]. However, in our study, obesity was not associated with a lack of adherence to the thromboprophylaxis protocol. Similarly, surgical factors that might be expected to influence adherence to prophylaxis, including intraoperative blood loss and the radicality of the operation, were not associated.

The final significant barrier to compliance with postoperative VTE prophylaxis protocol is the requirement for daily, and sometimes twice-daily, subcutaneous injections of LMWH or unfractionated heparin. Direct oral anticoagulants (DOACs) offer a major advantage over LMWH, as they are administered orally rather than parenterally, which may improve patient adherence[26]. The VALERIA trial, which compared rivaroxaban to enoxaparin for thromboprophylaxis following major gynecological cancer surgery, supported the hypothesis that DOACs could be a promising alternative to LMWH in this high-risk population. However, the statistical power of the study was limited due to not reaching the intended sample size[27]. However, DOACs are not currently reimbursed in Thailand and remain relatively expensive, limiting their accessibility. Despite this, DOACs offer greater convenience and may significantly improve patient compliance, particularly among those who prefer oral medication to daily injections.

Based on our finding of poor adherence, additional strategies are needed to improve compliance with VTE prophylaxis protocols. These include conducting audits after the implementation of ERAS protocols, which are associated with a reduced risk of perioperative complications, including VTE[28], quality improvement initiatives within gynecologic oncology services[29] and the integration of risk assessment and risk-based prophylaxis systems into electronic medical records for all surgical patients[30]. Additionally, factors unique to Thailand, such as patient acceptance of prolonged home injections and physician awareness or attitudes toward guideline adherence, should be further explored.

The limitations of our study included its retrospective nature and the absence of data on the actual incidence of VTE in our cohort. A key strength was that the study reflects real-world adherence rates at our institution following the implementation of the ERAS protocol.

Despite strong international guidelines and robust clinical evidence supporting extended-duration VTE prophylaxis in high-risk gynecologic cancer patients, especially in the ERAS period, adherence remains suboptimal. Our study revealed that only 22% of patients received complete prophylaxis as recommended. Improving adherence will require a multifaceted approach, particularly the implementation of new strategies and systems within our institution. Strengthening these measures is essential to improve patient safety and reduce the incidence of postoperative VTE in this high-risk population.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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