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EDITORIAL

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

Vorapong Phupong, M.D., FRTCOG.*

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

This first issue of Thai Journal of Obstetrics and Gynaecology 2026 contains many interesting articles. The special article is "Evolution and prospects of educational pathways in invasive prenatal procedures". The topics included current landscape of training, gaps and needs, and future trajectory[1].

This issue also contains seven original articles. kanthiya performed a cross-sectional study to evaluate the prevalence of anxiety and depression in women with abnormal cervical cytology referred for colposcopy at Suratthani Cancer Hospital and identify associated risk factors. The results showed psychological distress was common among women referred for colposcopy, with significant predictors including smoking, poor disease knowledge, and co-existing anxiety[2].

Kosidapan et al performed a prospective cohort study to evaluate the efficacy of oral iron supplementation on the resolution of anemia and the improvement of hemoglobin (Hb) levels in anemic pregnant women with abnormal Hb typing results compared to those with normal Hb typing results. They found an additional oral iron supplementation did not significantly correct anemia in pregnant women with abnormal Hb typing who were most likely thalassemia carriers[3].

Tueman et al performed a randomized controlled trial to study the effect of 2% lidocaine gel in conjunction with ibuprofen for pain relief during endometrial biopsy. They found the addition of 2% lidocaine gel was effective in reducing pain during endometrial biopsy when compared to ibuprofen alone[4].

Eiamcharoenlap et al performed a retrospective case-control study to investigate maternal factors associated with early-onset neonatal sepsis in preterm infants at Maharat Nakhon Ratchasima Hospital. They found gestational age < 34 weeks, maternal chorioamnionitis, and maternal leukocytosis were significant risk factors associated with early-onset neonatal sepsis in preterm neonates[5].

Pichaipaet et al performed a randomized controlled trial to compare blood glucose levels and patient satisfaction during gestational diabetes screening between two oral glucose formulations: 50 grams of dissolved glucose powder in water versus 50% intravenous glucose solution diluted for oral intake. The result showed the administration of 50 grams of glucose powder dissolved in water and 100 milliliters of 50% injectable glucose solution diluted to a total volume of 300 milliliters resulted in no significant difference in 1-hour post-load plasma glucose levels[6].

Ariyasriwatana et al performed a retrospective study to determine disease-free survival, disease-specific survival and lymph node metastasis in human papilloma virus (HPV) - associated cervical adenocarcinoma by

pattern-based classification. They found the 5-year disease-specific survival was 100% with no lymph node metastasis in patients with pattern A. Patients with pattern B and C were associated with higher risk of lymphovascular space invasion and lymph node metastasis[7].

Saengsiriwudh, et al performed a retrospective study to evaluate the association between low pregnancy-associated plasma protein-A (PAPP-A) levels and preterm birth and to assess the relationship between low PAPP-A levels and other adverse pregnancy outcomes, as well as analyzing factors affecting PAPP-A levels. The results revealed that low PAPP-A levels were significantly associated with preterm birth, gestational hypertension, and fetal growth restriction[8].

For the coming new year 2026, we would like to extend our warmest wishes to all members of Royal Colleague of Obstetricians and Gynaecologists, editorial board, reviewers, authors and families. We thank to all the authors, readers, reviewers, and editors for your great contributions to Thai Journal of Obstetrics and Gynaecology this past year and look forward to receiving your invaluable contributions in new year 2026.

Happy New Year 2026

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SPECIAL ARTICLE

Evolution and Prospects of Educational Pathways in Invasive Prenatal Procedures

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ABSTRACT

Invasive prenatal procedures (IPPs) are integral to the practice of perinatology. The most commonly performed diagnostic procedures include chorionic villus sampling, amniocentesis, and percutaneous umbilical blood sampling. These techniques require precise hand–eye coordination under real-time ultrasonographic guidance. Fetal therapeutic procedures demand even more advanced skills, combining real-time ultrasound guidance with endoscopic surgical techniques. Structured training is essential to minimize procedure-related complications, particularly among less experienced operators. Teaching methods generally include simulation, animal models, mentorship–apprenticeship, and curriculum-based workshops. Simulation-based training employs both low-fidelity box trainers and high-fidelity virtual reality systems. Animal model training offers several advantages over ex-vivo synthetic simulators. Pregnant sheep provide the most realistic model for training and for developing novel in-utero surgical techniques because of their suitable uterine volume and fetal size. However, the cost and ethical concerns remain major limitations. Mentorship–apprenticeship typically begins with observation, followed by hands-on training and progressive responsibility until independent performance. Hands-on workshops offer opportunities to refresh skills in infrequently performed procedures. The advent of non-invasive prenatal testing using cell-free fetal DNA analysis has significantly reduced the number of invasive diagnostic procedures. Consequently, training programs must adapt to these changing circumstances. This article aims to assess current training paradigms, identify existing gaps, and propose future directions for skill acquisition in IPPs.

Keywords: Invasive prenatal procedures, fetal therapy, surgical simulation, medical education, ultrasound guidance, skill acquisition

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Introduction

Modern fetal medicine practice encompasses a substantial component of invasive prenatal procedures (IPPs). Over the past decades, numerous invasive techniques have been introduced for fetal diagnosis and therapy. Diagnostic procedures such as chorionic villus sampling (CVS), amniocentesis, and percutaneous umbilical blood sampling (PUBS) are performed under real-time ultrasound guidance. Inexperienced operators often require time to develop proficient hand–eye coordination. Most diagnostic procedures are performed by a single operator with minimal assistance. The acquisition of new minimally invasive techniques commonly follows the traditional surgical mentorship–apprenticeship model, wherein trainees observe expert operators performing live procedures and eventually perform the techniques under supervision[1]. This time-honored model, however, limits knowledge transfer to one-on-one interactions and depends heavily on available resources, including training funds and patient caseloads.

Initial training for diagnostic procedures can be achieved using ex-vivo models. Therapeutic procedures pose greater challenges and require more advanced ultrasound-guided intervention skills. Moreover, teamwork becomes increasingly important in such settings. For instance, in fetal shunt placement, the operator must use both hands to deploy the shunt system while coordinating with the sonographer.

Fetoscopy was originally developed to guide fetal blood sampling from chorionic vessels but was soon replaced by ultrasound-guided PUBS. The treatment of twin-to-twin transfusion syndrome (TTTS) has renewed interest in fetoscopic interventions in recent years[2]. Fetoscopy is now most commonly used for selective laser ablation of chorionic anastomoses, the most effective treatment for severe mid-trimester TTTS, and has opened new avenues for research and development in minimally invasive fetal surgery.

Like all new invasive techniques, these procedures are associated with a learning curve, where success rates and complication rates improve with experience. The demand for surgeons capable of safely performing these procedures is increasing. This article comprises three main sections: (1) assessment of current training paradigms, (2) identification of existing gaps and needs, and (3) recommendations for future directions in skill acquisition for IPPs. The target audience includes maternal-fetal medicine fellows, obstetric and gynecology residents, fetal medicine teams, and educators in perinatal training.

Section 1: Current Landscape of Training

The current landscape of training in IPPs is evolving under dual pressures: declining procedural volumes and rising expectations for competence prior to independent practice. On one hand, advances in non-invasive prenatal testing (NIPT) and other minimally invasive diagnostics have reduced opportunities for hands-on training. Presently, training modalities include simulation, animal models, mentorship–apprenticeship, and curriculum-based workshops.

Simulation-based training

IPPs require precise hand-eye coordination under real-time ultrasound guidance. Fetoscopic procedures combine ultrasonographic and endoscopic skills, demanding simultaneous use of both modalities. Practice using appropriate instruments is vital to reducing unnecessary maternal and fetal morbidity, as complications tend to occur more frequently during

the early phase of the learning curve. Therefore, trainees must gain hands-on experience before performing these procedures under supervision.

Training should begin on models or simulators, enabling learners to practice maintaining the needle within the ultrasonic plane so that it remains visible throughout the procedure, ensuring safety[3]. Skill development can be facilitated using low-fidelity box trainers and high-fidelity virtual reality simulators. The term "fidelity" refers to how closely a simulation mimics real conditions, though its definition is not standardized in medical literature. Typically, "low fidelity" denotes simple, artificial setups, while "high fidelity" represents realistic, complex simulations[4].

Low-fidelity box trainer

Simplified models for training in invasive fetal diagnostic and therapeutic procedures can be constructed in-house. These models simulate the intrauterine environment, enabling trainees to develop proficiency conveniently. For centers where such procedures are infrequently performed, simulators help maintain technical skills[5].

A typical model consists of a plastic container with a rubber latex sheet at the base to prevent sonographic reverberation. A fresh placenta from seronegative donors is used, with the umbilical cord tied and chorionic vessels sutured at their distal ends to preserve vascular architecture. The placenta is rinsed and fixed to simulate either anterior or posterior placentation.

This model is simple, inexpensive, and effective for training in fetoscopic interventions such as selective photocoagulation of placental vessels. However, it has limitations, including biohazard risks, contamination of the endoscopic view by blood, and anatomical differences from monochorionic placentas.

High-fidelity virtual reality trainer

To address these limitations, an intrauterine endoscopic training model (Siriraj Fetoscopic Surgical Simulator™) was developed[6]. It consists of a soft rubber spherical structure representing a mid-trimester uterus with a monochorionic twin placenta mounted inside. The model allows infusion and drainage of water to simulate polyhydramnios associated with severe TTTS. It enables simultaneous sonographic and fetoscopic visualization, allowing trainees to practice mapping chorionic vasculature and handling fiber-optic scopes.

Three-dimensional printed models have recently been introduced to further enhance fidelity[7]. While these simulators allow realistic fluid manipulation and ultrasound imaging, they cannot replicate dynamic features such as fetal movement or actual laser coagulation.

Animal Model

Although simulator technologies are advancing, animal models remain valuable for training procedures that involve dynamic physiology, such as bleeding or uterine contractions. Pregnant sheep are the most commonly used species due to their uterine size and fetal dimensions, which approximate human conditions. Animal models enable trainees to manage intraoperative challenges, including amniotic bleeding, collapsed sacs, or fetal positioning, and to recognize complications such as amniotic leakage, bleeding, miscarriage, or fetal demise.

Animal models also allow testing of new interventions, such as intrauterine CO_2 insufflation or amniopatch application, and the creation of malformations like gastroschisis or meningomyelocele for corrective experiments[8-12].

Nevertheless, limitations include cost, anesthesia requirements, and ethical concerns. Sheep have a bicornuate uterus and a 145-day gestation[13]. Smaller models, such as pregnant rabbits, offer lower costs and fewer facility requirements[14]. Baboons have also been used to simulate complex fetal surgeries, such as intrauterine cleft lip repair[15].

The ethical considerations surrounding animal use necessitate strategies to minimize animal numbers, reduce costs, and prioritize the use of tissues from euthanized research animals[16].

Mentorship–apprenticeship

While simulation and animal models facilitate repetitive practice, they do not fully replicate teamwork dynamics or real-time decision-making. Direct procedural experience under supervision remains the most effective training modality[17]. Training begins with observation, progresses to assistance, and culminates in independent performance under guidance. Early procedures typically include "simple" amniocenteses or CVS cases. The number of procedures required to achieve proficiency varies, but most studies suggest diminishing returns after approximately 100 independent cases[3].

This model, however, faces limitations, including variability in trainee proficiency and ethical constraints on using certain cases for training. Although structured assessment systems exist, only a few centers have formal programs[18].

Curriculum-based workshops

Professional organizations have initiated curriculum-based workshops to address reduced procedural exposure due to NIPT and declining fertility rates[19]. Studies demonstrate that operator experience correlates with lower pregnancy loss rates[20, 21]. Simulation workshops remain valuable even for experienced providers by enabling skill maintenance in rarely performed procedures. This is one of the most important priorities for Disease-Specific Certification programs that ensure standardized care by verifying adherence to performance benchmarks and promoting interdisciplinary collaboration. These workshops facilitate sustained skill development through repeated, progressively challenging simulations with standardized performance metrics.

Section 2: Gaps and Needs

Efforts to accelerate the learning curve of IPPs persist, yet significant gaps remain in (1) competency benchmarks, (2) access inequality, (3) data-driven feedback, and (4) interdisciplinary integration.

Competency benchmarks

Despite IPPs being core components of fetal medicine training, standardized competency-based curriculum is lacking. Competence must be demonstrated through objective assessment rather than presumed based on years of experience[22]. The field is shifting toward competency-based, simulation-enhanced education, but evidence-based training standards are still needed.

Access inequality

Global disparities exist in surgical training quality and infrastructure, particularly between urban and rural areas. Key challenges include limited procedural exposure, uneven simulation access, and inadequate mentorship. International collaboration may help align best practices with local contexts[23].

Data-driven feedback

Traditional validation methods, such as logbooks and theoretical testing, inadequately measure procedural competency. Training programs are increasingly adopting structured curricula and objective assessment tools that provide real-time, data-driven feedback[24].

Interdisciplinary integration

Complex fetal therapeutic procedures require seamless collaboration among multidisciplinary teams, including anesthesiologists, neonatologists, and surgeons. Deficiencies in non-technical skills such as teamwork and communication contribute to adverse events. Multidisciplinary simulation training can mitigate these risks, though program implementation barriers persist[25].

Section 3: Future Trajectory

First-trimester NIPT has markedly decreased the demand for diagnostic IPPs despite rising maternal age at first pregnancy[26]. As with PUBS, procedures such as CVS and amniocentesis may

become centralized to a few specialized centers, limiting training opportunities. However, diagnostic IPPs remain necessary for specific cases, such as Mendelian disorders and high-risk screening results. Training must therefore remain adaptable, incorporating innovations, digital credentialing, tele-mentoring, and global registries.

Innovations

Advances in ultrasound, three-/four-dimensional imaging, and endoscopic simulation increasingly allow realistic training environments with minimal patient risk. The development of digital pregnancy models, supported by recent regulatory shifts, offers potential for sophisticated in-silico fetal research[27].

Digital credentialing

Blockchain-based systems can securely and transparently record skill verification, providing globally portable credentials for procedural competence[28].

Tele-mentoring

Augmented and virtual reality (AR/VR)-assisted tele-mentoring allows real-time remote supervision of procedures, improving access to expertise. The concept, first demonstrated in the 1960s via satellite-assisted surgery, continues to evolve with modern technology[29].

Global registries

Global registries can track procedural outcomes and training efficacy through digital dashboards, identifying disparities and guiding improvement[30]. These databases are especially valuable in therapeutic IPPs, where procedural volume remains low across most centers.

Conclusion

Training in IPPs is a critical and timely issue given the evolution of fetal therapy and increasing expectations for procedural competence. Current challenges include limited procedural opportunities, curricular variability, ethical concerns, and the absence of standardized assessment tools. Future directions should emphasize the development of an internationally endorsed core curriculum, cross-institutional fellowships, scalable simulation access, and research in procedural outcomes[31]. Ultimately, fostering adaptive expertise through competence-based education will enable future fetal medicine specialists to respond effectively to evolving clinical and ethical challenges[32].

Potential conflicts of interest

The authors declare no competing interests.

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GYNAECOLOGY

Anxiety and Depression in Women with Abnormal Cervical Cytology Referred for Colposcopy: A Study at Suratthani Cancer Hospital

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ABSTRACT

Objectives: To evaluate the prevalence of anxiety and depression in women with abnormal cervical cytology referred for colposcopy at Suratthani Cancer Hospital and identify associated risk factors.

Materials and Methods: In this cross-sectional analytic study, all women with abnormal cervical cytology referred for colposcopy at Suratthani Cancer Hospital between January 2025 and March 2025. Participants completed the Thai version of the hospital anxiety and depression scale (HADS). A score ≥ 11 on the anxiety (HADS-A) or depression (HADS-D) subscale was considered clinically significant and identified factors that associated to this group by multivariable logistic regression analysis.

Results: Total one hundred ninety-five women were participants. The mean age was 42.2 years (standard deviation 10.0). Clinically significant anxiety (HADS-A ≥ 11) was present in 15.4% of participants, and depression (HADS-D ≥ 11) in 5.6%. The only factors that significant associated with anxiety was depression ($p < 0.01$) and independent predictors of depression with multivariate regression analysis were smoking (adjusted odds ratio (aOR) 7.6, 95% confidence interval (CI) 2.20–98.72), poor cervical cancer knowledge (aOR 24.98, 95%CI 2.78–224.67), and concurrent anxiety (aOR 23.0, 95%CI 4.3–121).

Conclusion: Psychological distress was common among women referred for colposcopy, with significant predictors including smoking, poor disease knowledge, and co-existing anxiety. Integrating mental health screening and patient education into colposcopy care could improve psychological outcomes and care engagement.

Keywords: cervical cancer screening, colposcopy, anxiety, depression, HADS.

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ภาวะวิตกกังวลและซึมเศร้าในสตรีที่มีผลการตรวจคัดกรองมะเร็งปากมดลูกผิดปกติและได้รับการส่องกล้องคอลโปสโคปในโรงพยาบาลมะเร็งสุราษฎร์ธานี

กาญจนา กันธิยะ

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินระดับภาวะวิตกกังวลและภาวะซึมเศร้าในสตรีที่มีผลการตรวจคัดกรองมะเร็งปากมดลูกผิดปกติและได้รับการส่งต่อเพื่อส่องกล้องคอลโปสโคปในโรงพยาบาลมะเร็งสุราษฎร์ธานี และประเมินปัจจัยที่มีผลต่อภาวะวิตกกังวลและซึมเศร้า*

วัสดุและวิธีการ*: เป็นการศึกษาภาคตัดขวาง โดยนำสตรีที่มีผลการตรวจคัดกรองมะเร็งปากมดลูกผิดปกติและได้รับการส่งต่อเพื่อส่องกล้องคอลโปสโคปในโรงพยาบาลมะเร็งสุราษฎร์ธานี ระหว่างเดือนมกราคม 2568 ถึงมีนาคม 2568 ผู้เข้าร่วมศึกษาทำแบบประเมิน hospital anxiety and depression scale (HADS) ฉบับภาษาไทย และได้จำแนกคะแนนตั้งแต่ 11 คะแนนขึ้นไปในหมวดภาวะวิตกกังวล (HADS-A) หรือภาวะซึมเศร้า (HADS-D) ถือว่ามีอาการทางคลินิก และศึกษาปัจจัยที่มีผลต่อสตรีกลุ่มนี้โดยการวิเคราะห์ถดถอยโลจิสติกพหุคูณ*

ผลการศึกษา*: สตรีจำนวน 195 รายเข้าร่วมทำแบบสอบถามมีอายุเฉลี่ย 42.2 ปี พบว่าร้อยละ 15.4 มีภาวะวิตกกังวลและร้อยละ 5.6 มีภาวะซึมเศร้า ในระดับที่มีนัยสำคัญทางคลินิก และพบปัจจัยที่มีผลต่อภาวะนี้ โดยการวิเคราะห์เชิงเดียวพบว่าการสูบบุหรี่ ความรู้เกี่ยวกับมะเร็งปากมดลูกที่จำกัด และประวัติการตรวจคัดกรองที่ไม่สม่ำเสมอ มีความสัมพันธ์กับภาวะซึมเศร้า การวิเคราะห์ถดถอยโลจิสติกพหุคูณพบว่า การสูบบุหรี่ (adjusted odds ratio (aOR) 7.6, 95% confidence interval (CI) 2.20–98.72) ความรู้ที่ไม่เพียงพอเกี่ยวกับมะเร็งปากมดลูก (aOR 24.98, 95%CI 2.78–224.67) และอาการวิตกกังวลร่วม (aOR 23.0, 95%CI 4.3–121) เป็นปัจจัยพยากรณ์อิสระของภาวะซึมเศร้า*

สรุป*: ภาวะวิตกกังวลและภาวะซึมเศร้าพบได้บ่อยในสตรีที่มีผลการตรวจคัดกรองมะเร็งปากมดลูกผิดปกติและได้รับการส่งต่อเพื่อส่องกล้องคอลโปสโคปในโรงพยาบาลมะเร็งสุราษฎร์ธานี โดยมีปัจจัยที่สัมพันธ์ได้แก่ การสูบบุหรี่ ความรู้เกี่ยวกับโรคที่ไม่เพียงพอ และอาการวิตกกังวลร่วม จากข้อมูลนี้จะช่วยพัฒนาการบูรณาการการคัดกรองสุขภาพจิตและการให้ความรู้แก่สตรีก่อนการส่องกล้องคอลโปสโคปบริเวณปากมดลูก อาจช่วยลดภาวะเครียดและเพิ่มความร่วมมือในการรักษาได้*

คำสำคัญ*: การตรวจคัดกรองมะเร็งปากมดลูก, คอลโปสโคป (colposcopy), วิตกกังวล, ซึมเศร้า, HADS*

Introduction

Cervical cancer remains a significant public health concern and is the fourth most common cancer among women worldwide. In 2022, approximately 660,000 new cases and 350,000 related deaths were reported globally[1]. In Thailand, around 9,158 new cases and 4,705 deaths occur annually[2]. The high incidence and mortality rates are largely attributed to the lack of effective screening programs and limited coverage of existing services[3-4].

Persistent infection with high-risk types of human papillomavirus (HPV), particularly types 16 and 18, is the primary cause of cervical cancer, accounting for approximately 70% of cases[5]. Current screening methods include cytology and HPV testing. In Thailand, campaigns promoting HPV deoxyribonucleic acid (DNA) self-sampling have led to increased detection of HPV infections. According to data from the National Cancer Institute, the proportion of women with abnormal screening results rose from 1.13% to 1.53% between 2010 and 2014, with 6–7% requiring colposcopy[6].

Colposcopy is a procedure that enables magnified visualization of the cervix is essential for evaluating abnormal findings and guiding further management, such as biopsy, cryotherapy, or cauterization. However, the procedure can cause considerable psychological distress[7]. A study in Thailand reported significantly higher anxiety and depression levels among women referred for colposcopy due to abnormal cytology[8]. Despite this, healthcare providers often underestimate the psychological burden, potentially exacerbating patient anxiety. Elevated anxiety can impair cognitive processing, hinder understanding of medical information, and contribute to negative perceptions of care[9-10]. These effects may reduce compliance with appointments and increase discomfort during the procedure.

The aim of this study was to assess anxiety and depression levels in women undergoing colposcopy after abnormal cervical cytology and to identify factors that predict heightened anxiety. The findings may inform strategies to better support at-risk patients and improve overall care delivery.

Materials and Methods

A cross-sectional analytic study was conducted to assess the level of anxiety in women with abnormal cervical cancer screening results undergoing colposcopy at Suratthani Cancer Hospital between January 2025 and March 2025. The study was approved by the Institutional Review Board, and both verbal and written informed consent were obtained from all participants.

Inclusion criteria were 18 or more-year-old women with abnormal cervical cytology results and undergoing colposcopy at Suratthani Cancer Hospital. Exclusion criteria were women inability to communicate in Thai or incomplete survey responses (i.e., more than two unanswered questions).

Anxiety and depression symptoms were assessed using the Thai version of the hospital anxiety and depression scale (HADS), a self-administered questionnaire. The HADS consists of 14 items, divided into two subscales: seven items for anxiety (HADS-A) and seven for depression (HADS-D). Each item is scored on a 4-point Likert scale (0–3), resulting in subscale scores ranging from 0 to 21. The scores are categorized as follows:

0–7: no anxiety or depression, 8–10: mild symptoms, not considered a definitive psychiatric disorder, 11–21: moderate to severe symptoms, considered indicative of a psychiatric disorder[11-12].

Internal consistency of the subscales was assessed using Cronbach's alpha. Participants completed the questionnaire independently while waiting for their colposcopy procedure.

The sample size was calculated using the formula for descriptive studies, assuming a 95%

confidence level (CI), 2% margin of error, and the proportion of women undergoing colposcopy based on a study by Chait et al[13]. A minimum of 160 participants was required. To account for potential dropouts or incomplete data, the sample size was increased by 10%, yielding a final target of 180 participants.

Demographic and clinical data were collected, including age, marital status, religion, comorbidities, smoking history, number of sexual partners, psychiatric history, cancer history, family history of cancer, income, education level, self-assessed cervical cancer and colposcopy understanding, waiting time for colposcopy, and cervical screening results.

The primary outcome was the prevalence of anxiety symptoms, defined as a HADS-A score > 11. The secondary outcome was the prevalence of depression, defined as a HADS-D score > 11. Multivariate regression analysis was used to identify predictors of anxiety.

Statistical analysis was performed using Stata® version 12. Descriptive statistics were used to summarize the data: categorical variables were presented as frequencies and percentages, and continuous variables as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. A p value < 0.05 was considered statistically significant. Chi-square test and independent t test were used for univariate regression analysis. Variables with $p < 0.05$ were entered into multivariate regression analysis to identify independent factors associated with anxiety (HADS-A) and depression (HADS-D).

Results

A total of 195 women referred for colposcopy following abnormal cervical cytology at Suratthani Cancer Hospital were included in the study. The demographic and characteristics are shown in Table 1. The mean age of participants was 42.2 years (SD 10.0), ranging from 18 to 65 years. Regarding marital status, 50.3% (n = 98) were married, 28.7% (n = 56) single, 7.7% (n = 15) divorced, and 13.3% (n = 26) widowed. Most participants identified as Buddhist (97.4%, n = 190), with smaller proportions identifying as Muslim (2.1%, n = 4) or Christian (0.5%, n = 1).

Educational levels were relatively balanced, with 46.7% (n = 91) having completed university education and 53.3% (n = 104) having less than university-level education. The majority (77.9%, n = 152) reported a monthly income above 10,000 Baht. Two-thirds (66.7%, n = 130) were parous, and 55.9% (n = 109) reported having more than one lifetime sexual partner. Only 2.6% (n = 5) were current smokers.

In terms of health history, 21.1% (n = 47) had at least one chronic medical condition, and 2.6% (n = 5) reported a history of depression. The personal history of cancer was rare (7.7%, n = 15), with cervical cancer being the most common (5.1%, n = 10). A family history of cancer was reported by 39.0% (n = 76). Only 15.9% (n = 31) had received HPV vaccination. Knowledge of cervical cancer was generally low: 24.1% (n = 47) reported no knowledge, and 42.6% (n = 83) reported limited understanding. Similarly, 48.7% (n = 95) had no prior knowledge of colposcopy. With regard to screening history, 32.8% (n = 64) had never undergone cervical cancer screening, 45.6% (n = 89) reported regular screening, and 21.5% (n = 42) reported occasional screening.

Psychological assessment using the HADS revealed mean anxiety and depression scores of 6.4 (SD 3.9) and 3.5 (SD 3.3), respectively. Clinically significant anxiety (HADS-A ≥ 11) was identified in 15.4% (n = 30), and clinically significant depression (HADS-D ≥ 11) in 5.6% (n = 11). Most participants (76.9%, n = 150) waited less than one month for colposcopy.

Table 1. Demographic and clinical characteristics of participants (n = 195).

Characteristics	n = 195 (%)
Age (years), mean ± SD	42.2 ± 10.0
Marital status,	56 (28.7%)
Single	98 (50.3%)
Married	15 (7.7%)
Divorced	26 (13.3%)
Widow	0.068
Smoking	5 (2.6%)
Sex partner	
1	86 (44.1%)
> 1	109 (55.9%)
Parity	130 (66.7%)
Comorbidity	47 (21.1%)
History of depression	5 (2.6%)
History of Cancer	
No	180 (92.3%)
Cervical cancer	10 (5.1%)
Breast cancer	2 (1.0%)
Other cancer	3 (1.5%)
Family history	
No	119 (61.0%)
Yes	76 (39.0%)
Religion	
Buddhist	190 (97.4%)
Christ	1 (0.5%)
Muslim	4 (2.1%)
Education	
University level	91 (46.7%)
Below university level	104 (55.3%)
HPV Vaccine	31 (15.9%)
Cervical cancer understanding	
None	47 (24.1%)
Little	83 (42.6%)
Moderate	64 (32.8%)
Good	1 (0.5%)
Colposcopy understanding	
None	95 (48.7%)
Little	72 (36.9%)
Moderate	27 (13.8%)
Good	1 (0.5%)
Income (Baht/month)	
< 10,000	43 (22.1%)
> 10,000	152 (77.9%)
History of Pap smear	
routine	89 (45.6%)
occasional	42 (21.5%)
Never before	64 (32.8%)
Waiting time	
< 1 month	150 (76.9%)
> 1 month	45 (23.1%)
HADS-A score, mean (SD)	6.4 (3.9)
HADS-A score ≥ 11	30 (15.4%)
HADS-D score, mean (SD)	3.5 (3.3)
HADS-D score ≥ 11	11 (5.6%)

Baseline demographic and clinical data of women referred for colposcopy after abnormal cervical cytology.
Data are shown as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables.
HPV: human papilloma virus, HADS-A: hospital anxiety and depression scale – anxiety subscale, HADS-D: hospital anxiety and depression scale – depression subscale

Univariate regression analysis showed only HADS-D score was associated with anxiety ($p < 0.01$) and no significant associations between anxiety and demographic or clinical factors, including age, marital status, income, education, parity, smoking status, or comorbidities. Although not statistically significant, occasional/never cancer screening tended to be associated with anxiety (66.7% vs 52.7%, $p = 0.15$) (Table 2).

Table 2. Univariate analysis of factors associated with clinically significant anxiety (HADS-A ≥ 11).

Factor	HADS-A ≥ 11 (n = 30)	HADS-A < 11 (n = 165)	p value
Age (years), mean ± SD	40.7 ± 9.5	42.5 ± 10.1	0.35
Marital status			0.38
Married	19 (63.3%)	79 (47.8%)	
Single	6 (20.0%)	50 (30.3%)	
Widow/Divorced	5 (16.7%)	36 (21.8%)	
Parity	20 (66.7%)	110 (66.6%)	0.55
Smoking	1 (3.3%)	4 (2.4%)	0.57
Lifetime sexual partners			0.45
1	14 (46.7%)	72 (43.6%)	
≥ 2	16 (53.3%)	93 (56.3%)	
Underlying disease	8 (26.7%)	39 (23.6%)	0.72
History of malignancy	1 (3.3%)	19 (11.5%)	0.19
History of depression	1 (3.3%)	4 (2.4%)	0.57
Family history of cancer	10 (33.3%)	66 (40.0%)	0.88
HPV vaccination	5 (16.7%)	26 (15.7%)	0.54
Religion			0.56
Buddhist	29 (96.7%)	161 (97.5%)	
Other	1 (3.3%)	4 (2.4%)	
Education			0.27
University level	12 (40.0%)	79 (47.8%)	
Below university level	18 (60.0%)	86 (52.1%)	
Income ≥ 10,000 THB	22 (73.3%)	130 (78.7%)	0.32
Waiting time > 1 month	5 (16.7%)	40 (24.2%)	0.25
Cervical cancer knowledge			0.39
None/Low	23 (76.7%)	107 (64.8%)	
Medium/Good	7 (23.3%)	58 (35.1%)	
Colposcopy knowledge			0.45
None/Low	27 (90.0%)	140 (84.8%)	
Medium/Good	3 (10.0%)	25 (15.1%)	
Cervical cancer screening			0.15
Routine	10 (33.3%)	78 (47.2%)	
Occasional/Never	20 (66.7%)	87 (52.7%)	
HADS-D ≥ 11	3 (1.8%)	8 (4.8%)	< 0.01

Comparison of demographic, clinical, and psychosocial factors between women with and without clinically significant anxiety symptoms based on HADS-A scores. P values were calculated using chi-square test for categorical variables and independent t-test for continuous variables.
HPV: human papilloma virus, HADS-A: hospital anxiety and depression scale – anxiety subscale, HADS-D: hospital anxiety and depression scale – depression subscale

In contrast, depression (HADS-D ≥ 11) was significantly associated with smoking status (p = 0.02), limited knowledge of cervical cancer (p = 0.01), and lack of routine cervical screening (p =

0.05) (Table 3). Multivariate regression analysis identified three independent predictors of depression: current smoking (adjusted odds ratio [aOR] 7.6, 95%CI 2.20–98.72; p < 0.01), limited cervical cancer knowledge (aOR 24.98, 95%CI 2.78–224.67; p = 0.01), and concurrent clinically significant anxiety (aOR 23.0, 95%CI 4.3–121.0; p < 0.01) (Table 4).

Table 3. Univariate analysis of factors associated with clinically significant depression (HADS-D ≥ 11).

Factor	HADS-D ≥ 11 (n = 11)	HADS-D < 11 (n = 184)	p value
Age (years), mean ± SD.	41.4 ± 7.7	42.3 ± 10.2	0.78
Marital status			0.68
Married	7 (63.6%)	91 (49.5%)	
Single	3 (27.3%)	53 (28.8%)	
Widow/Divorced	1 (9.1%)	40 (21.7%)	
Parity	7 (63.6%)	123 (66.8%)	0.82
Smoking	2 (18.2%)	3 (1.6%)	0.02*
Lifetime sexual partners			0.47
1	6 (54.5%)	80 (43.5%)	
≥ 2	5 (45.5%)	104 (56.5%)	
Underlying disease	3 (27.3%)	44 (23.9%)	0.80
History of malignancy	0 (0.0%)	15 (8.2%)	0.32
History of depression	0 (0.0%)	5 (2.7%)	0.58
Family history of cancer	2 (18.2%)	74 (40.2%)	0.12
HPV vaccination	2 (18.2%)	29 (15.8%)	0.56
Religion			0.92
Buddhist	10 (90.9%)	180 (97.8%)	
Other	1 (9.1%)	4 (2.2%)	
Education			0.15
University level	3 (27.3%)	88 (47.8%)	
Below university level	8 (72.7%)	96 (52.2%)	
Income ≥ 10,000 THB	7 (63.6%)	145 (78.8%)	0.20
Waiting time > 1 month	3 (27.3%)	42 (22.8%)	0.73
Cervical cancer knowledge			0.01*
None/Low	11 (100.0%)	119 (64.7%)	
Medium/Good	0 (0.0%)	65 (35.3%)	
Colposcopy knowledge			0.60
None/Low	10 (90.9%)	157 (85.3%)	
Medium/Good	1 (9.1%)	27 (14.7%)	
Cervical cancer screening			0.05*
Routine	2 (18.2%)	86 (46.7%)	
Occasional/Never	9 (81.8%)	98 (53.3%)	
HADS-A ≥ 11	8 (72.7%)	22 (12.0%)	< 0.01*

Comparison of demographic, clinical, and psychosocial factors between women with and without clinically significant depression symptoms based on HADS-D scores. P values were calculated using chi-square test for categorical variables and independent test for continuous variables.
HPV: human papilloma virus, HADS-A: hospital anxiety and depression scale – anxiety subscale, HADS-D: hospital anxiety and depression scale – depression subscale

Table 4. Multivariable logistic regression analysis of factors associated with clinically significant depression (HADS-D ≥ 11).

Factors	Adjusted odds ratio	95% CI	p value
Smoking	7.6	2.20, 98.72	< 0.01*
Cervical cancer knowledge	24.98	2.78, 224.67	0.01*
Cervical cancer screening	4.1	0.3, 10.3	0.06
HADS-A score ≥ 11	23.0	4.3, 121	< 0.01*

Results of multivariable logistic regression identifying independent predictors of clinically significant depression (HADS-D ≥ 11). Variables included were those with $p < 0.05$ in univariate analysis.
CI: confidence interval, HADS-A: hospital anxiety and depression scale – anxiety subscale, HADS-D: hospital anxiety and depression scale – depression subscale

Discussion

This study evaluated psychological distress in women referred for colposcopy after abnormal cervical cytology in a Thai tertiary cancer center. Using the HADS, we found that 15.4% of participants exhibited clinically significant anxiety and 5.6% met the threshold for depression. These findings aligned with previous research in both Thai and international settings, highlighting the psychological vulnerability associated with abnormal cytological findings and diagnostic colposcopy[8,13].

Consistent with our aim to identify predictors of psychological distress, we found that current smoking, limited knowledge about cervical cancer, and co-existing anxiety were independently associated with depressive symptoms. Although we observed significant wide confidence intervals reflect limited precision of the estimates. This imprecision is likely due to small sample size and low event rate, which reduces the statistical stability of the odds ratio.

Smoking's association with depression has been widely reported[14], and our findings reinforce the potential of smoking history as a clinical flag for emotional vulnerability in this setting and support smoking cessation. Knowledge deficits also played a significant role in mental health outcomes. Women with little or no understanding of cervical cancer were far more likely to experience depression. This supports evidence suggesting that uncertainty about medical conditions, particularly cancer, significantly contributes to distress and impairs emotional resilience[4,7,15]. Given the relatively high proportion of women in our study with limited knowledge of cervical cancer and colposcopy. We should improve patient education as part of pre-procedure counseling.

In our study, HADS-A score and HADS-D score were associated with each other. This supports the critical relationship between anxiety and depression, and it is important to emphasize that the presence of comorbid anxiety symptoms and disorders matters in relation to treatment[16].

Interestingly, social and demographic factors including age, income, education, and marital status were not significantly associated with anxiety in this study and other Thai literatures[8,17]. This finding diverges from some studies conducted in Western populations, where lower socioeconomic status and younger age have been linked to increased distress[10]. Several factors may explain this discrepancy. First, the relative homogeneity of our sample, particularly in terms of socioeconomic background, may have reduced the variability needed to identify significant predictors. Second, anxiety was measured at a single point immediately before colposcopy, which likely reflected situational distress and may have masked the influence of more stable sociodemographic predictors. Third, cultural factors may play a role: Thai women may experience anxiety differently than women in Western settings, possibly due to differing perceptions of illness, support systems, and coping strategies.

While many participants reported poor

understanding of colposcopy, this variable was not independently associated with psychological outcomes. It is possible that anxiety is more closely tied to perceptions of cancer risk rather than the diagnostic procedure itself, echoing prior studies showing that the emotional burden often stems from fear of cancer rather than procedural discomfort[7,13].

Our study benefits from a prospective design, use of a validated screening tool (HADS-T)[11], and a well-defined sample. However, limitations include it was a single center study which limited generalizability and possible selection bias. Its cross-sectional nature, which prevents causal inference, and the modest number of patients who met criteria for anxiety and depression, which may limit statistical power. Further studies with larger sample sizes are warranted to provide more reliable estimates. Additionally, reliance on self-reported data may introduce bias.

Our findings indicated that a significant proportion of women referred for colposcopy experience emotional distress, with smoking, poor cancer knowledge, and anxiety serving as key predictors of depression. These results highlight the importance of integrating psychological and educational interventions into cervical cancer diagnostic pathways to improve patient outcomes and engagement with care.

Conclusion

A substantial proportion of women referred for colposcopy following abnormal cervical cytology experienced clinically significant anxiety and, to a lesser extent, depression. Independent predictors of depression included smoking, poor knowledge of cervical cancer, and concurrent anxiety symptoms. These findings underscore the importance of integrating psychological screening and education into colposcopy services. Tailored interventions addressing patient knowledge and mental well-being may improve care experiences and compliance with follow-up. Further studies should explore the effectiveness of pre-procedure counseling and mental health support in reducing emotional distress among this population.

Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Efficacy of Oral Iron Supplementation in Anemic Pregnant Women with Normal and Abnormal Hemoglobin Typing

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ABSTRACT

Objectives: To evaluate the efficacy of oral iron supplementation on the resolution of anemia and the improvement of hemoglobin (Hb) levels in anemic pregnant women with abnormal Hb typing results compared to those with normal Hb typing results.

Materials and Methods: A prospective cohort study was conducted among pregnant women diagnosed with anemia (Hb < 11 g/dL in the first and third trimesters, or < 10.5 g/dL in the second trimester). Participants were classified according to Hb typing results (normal vs abnormal) and received additional oral iron supplementation exceeding the standard prenatal dosage. Routine antenatal blood tests were performed before and after supplementation.

Results: A total of 66 participants were enrolled (31 in the abnormal Hb typing group and 35 in the normal group). After exclusion, 57 participants remained for analysis, including 29 in the abnormal group and 28 in the normal group. Baseline characteristics did not differ significantly between groups. Among them, 8 participants (27.59%) in the abnormal group and 20 participants (71.43%) in the normal group achieved resolution of anemia ($p = 0.01$). In the abnormal group, the overall Hb level increased slightly, with a mean change of 0.49 g/dL versus 1.87 g/dL in the normal group which was significantly difference ($p < 0.001$).

Conclusion: Additional oral iron supplementation did not significantly correct anemia in pregnant women with abnormal Hb typing who were most likely thalassemia carriers. However, a modest increase in Hb levels was observed. Further studies are warranted to determine the optimal regimen of iron supplementation to achieve greater improvements in Hb levels in this group of women.

Keywords: iron supplementation, anemia, pregnancy, thalassemia trait.

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ประสิทธิผลของการใช้ยาเสริมธาตุเหล็ก เพื่อรักษาภาวะโลหิตจางในหญิงตั้งครรภ์ที่ผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติ

วรรธนัย โฆษิดาพันธุ์, ณัฐนันท์ วิไลเรืองชูวงษ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิผลของยาเสริมธาตุเหล็ก ในการรักษาภาวะโลหิตจาง และการเปลี่ยนแปลงของระดับฮีโมโกลบินในหญิงตั้งครรภ์ที่มีผลตรวจวิเคราะห์ฮีโมโกลบิน (Hb typing) ผิดปกติเทียบกับผู้ที่มีผลปกติ*

วัสดุและวิธีการ: *การวิจัยเชิงวิเคราะห์ ที่ติดตามบุคคลแบบไปข้างหน้าในหญิงตั้งครรภ์ที่ได้รับการวินิจฉัยภาวะโลหิตจาง (ระดับฮีโมลโกลบินน้อยกว่า 11 กรัมต่อเดซิลิตร ในไตรมาสที่ 1 และ 3, หรือน้อยกว่า 10.5 กรัมต่อเดซิลิตร ในไตรมาสที่ 2) แบ่งกลุ่มโดยขึ้นอยู่กับผลตรวจวิเคราะห์ฮีโมโกลบิน (ปกติ หรือ ผิดปกติ) และผู้เข้าร่วมวิจัยจะได้รับยาเสริมธาตุเหล็กเสริมจากยาบำรุงครรภ์ปกติ จากนั้นทำการบันทึก และวิเคราะห์ผลตรวจเลือดประจำของหญิงตั้งครรภ์ก่อน และหลังการได้รับยาเสริมธาตุเหล็ก*

ผลการศึกษา: *จากผู้ร่วมวิจัยทั้งหมด 66 คน (31 คนในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติ และ 35 คนในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินปกติ) คงเหลือในการวิเคราะห์ 57 คน แบ่งเป็น 29 คนในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติ และ 28 คนในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินปกติ ลักษณะพื้นฐานเมื่อเริ่มต้นการศึกษาไม่มีความแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่ม ผู้เข้าร่วมวิจัย 8 คน (ร้อยละ 27.59) ในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติ และ 20 คน (ร้อยละ 71.43) ในกลุ่มปกติ หายจากภาวะโลหิตจาง ($p = 0.01$) ในกลุ่มผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติพบว่าระดับฮีโมโกลบินเพิ่มขึ้นเล็กน้อย โดยค่าเฉลี่ยที่ 0.49 กรัมต่อเดซิลิตร เทียบกับกลุ่มผลตรวจปกติมีค่าเฉลี่ย 1.87 กรัมต่อเดซิลิตร ซึ่งแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$)*

สรุป: *การได้รับยาเสริมธาตุเหล็กเสริมจากยาบำรุงครรภ์ปกติไม่ได้ประสิทธิภาพดีอย่างมีนัยสำคัญ ในการรักษาภาวะโลหิตจางในหญิงตั้งครรภ์ที่มีผลตรวจวิเคราะห์ฮีโมโกลบินผิดปกติซึ่งน่าจะเป็นพาหะธาลัสซีเมีย อย่างไรก็ตามระดับฮีโมโกลบินมีแนวโน้มเพิ่มขึ้นได้เล็กน้อย การศึกษาเพิ่มเติมถึงปริมาณของยา ระยะเวลาการให้ยา และวิธีการบริหารยา อาจช่วยให้ระดับฮีโมโกลบินเพิ่มขึ้นได้ดีขึ้นในหญิงกลุ่มนี้*

คำสำคัญ: *ยาเสริมธาตุเหล็ก, ภาวะโลหิตจาง, ตั้งครรภ์, พาหะธาลัสซีเมีย*

Introduction

Anemia is a major global health concern and is one of the most common complications during pregnancy. In 2023, the World Health Organization (WHO) reported that 35.5% of pregnant women worldwide were affected by anemia[1]. In Thailand, the prevalence is 15.9% and has not significantly declined in recent years[2]. Anemia is associated with adverse maternal and neonatal outcomes, including fetal growth restriction, low Apgar scores, and perinatal mortality[3]. The most common causes in Thailand are iron deficiency anemia (IDA) and thalassemia[4-6].

Anemia in pregnancy is defined as hemoglobin (Hb) below 11 g/dL in the first and third trimesters and below 10.5 g/dL in the second trimester. IDA can be diagnosed through abnormal biochemical results, an Hb increase of more than 1 g/dL after treatment, or absent iron stores in a bone marrow smear[7].

Thalassemia is an autosomal recessive disorder that causes defective synthesis of α- or β- hemoglobin chains. Thalassemia disease includes β-thalassemia major ($\beta 0/\beta 0$), β-thalassemia/Hb E disease ($\beta 0/\beta E$), and Hb H disease (--/-α). Thalassemia traits (minor) comprise other genotypes[8] and are generally asymptomatic and require no treatment; however, carriers often present with microcytic red blood cells or mild anemia[9].

In Thailand, antenatal care (ANC) guidelines recommend thalassemia screening to identify carriers at risk of having offspring with severe thalassemia disease. Initial screening uses a complete blood count (CBC), with mean corpuscular volume (MCV) below 80 fL suggesting α-thalassemia 1 or β thalassemia carriers. The dichlorophenolindophenol precipitation (DCIP) test screens for Hb E carriers, while hemoglobin typing with an Hb A2 level of more than 3.5% is considered abnormal and indicative of carriers[8, 10].

Iron supplementation is recommended for most pregnant women. Nonetheless, it is not appropriate for women with certain thalassemia diseases (and in some ethnic groups, for those with hemochromatosis or other conditions associated with high iron load). In the absence of contraindication, iron is typically supplemented as ferrous gluconate, sulfate, or fumarate, at a minimum dose of 30 mg/day[10]. Additional supplementation may be prescribed for anemia, but the optimal dosage and duration remain uncertain[7]. Importantly, there are no specific recommendations for anemic pregnant women with thalassemia trait. Although thalassemia-related anemia is not caused by iron deficiency[8], pregnancy itself increases the risk of both anemia and iron deficiency due to normal physiological changes[3]. Moreover, even latent iron deficiency (the presence of iron deficiency without concurrent anemia) can lead to adverse neonatal outcomes[6]. Furthermore, some studies suggest iron may benefit women with β-thalassemia trait, because their anemia is primarily caused by ineffective erythropoiesis rather than hemolysis[3], but clinical evidence is limited.

This research aimed to evaluate the efficacy of oral iron supplementation in resolving anemia and improving Hb levels in anemic pregnant women with abnormal Hb typing results, presumed to represent thalassemia trait, compared with those with normal Hb typing. The results may guide strategies to reduce its incidence and ultimately support more effective ANC practices to improve maternal and neonatal outcomes.

Materials and Methods

This prospective cohort study was conducted at the ANC clinic, Chonburi Hospital, Chonburi, Thailand, between October 2024 and August 2025. The study protocol was approved by the Institutional Review Board of Chonburi Hospital (IRB-CBH; No. 53/67/R/h3), and informed consent was obtained from all participants.

Pregnant women diagnosed with anemia defined by Hb criteria[7] from routine laboratory tests during their first ANC visit were enrolled. In line with Chonburi Hospital ANC practice guidelines, participants received additional iron supplementation: ferrous fumarate tablets (FF) (200 mg/tablet; equivalent to 66 mg elemental iron[7]), one tablet twice daily. Participants continued with routine ANC and their compliance was checked by counting the remaining iron tablets in each ANC visit until the second routine laboratory investigation, after which the study follow-up ended, but FF was prescribed until delivery or anemia resolution.

The participants had inclusion criteria as follows: singleton pregnancy; follow-up with routine blood tests at Chonburi Hospital; Hb levels at the first visit below 11 g/dL for the first and third trimesters and below 10.5 g/dL for the second trimester; receipt of additional iron supplementation for at least 4 consecutive weeks before the second routine investigation; and medical compliance exceeding 80%, calculated as follows: the number of dispensed FF tablets minus the number of tablets returned at the follow-up visit, divided by the total number of prescribed days. For example, if a participant was dispensed 100 FF tablets and returned 60 tablets after 28 days, the compliance was calculated as (100 – 60) ÷ 28 = 1.43 tablets per day (71.43%).

Exclusion criteria were: thalassemia diseases, polycythemia, other hematological diseases, blood loss or transfusion during pregnancy, infectious diseases affecting Hb levels (dengue, human immunodeficiency virus, or hepatitis), chronic obstructive pulmonary disease, chronic kidney disease, chronic alcohol consumption, active smoking, abortion, intolerance to FF side effects, or drug allergy.

Participant information and laboratory results were collected from the electronic medical record system, including age, gestational age (GA), gravidity, parity, nationality, Hb typing, Hb levels from the first and second routine laboratory investigations, duration of FF intake, and compliance. Participants were divided into two groups based on Hb typing: normal versus abnormal. The primary outcome was to compare the number of anemic pregnant women achieving anemia resolution by Hb criteria[7] between the abnormal Hb typing group and the normal Hb typing group. The secondary outcome was the change in Hb level before and after additional iron supplementation between groups. (Tabel 1)

Table 1. Type of Hb typing in this study.

Type	n = 57 (100%)
Normal Hb typing	28 (49.12)
Hb E trait with or without alpha thalassemia	13 (22.81)
Homozygous Hb E with or without alpha thalassemia	11 (19.30)
Beta thalassemia trait with or without alpha thalassemia	2 (3.51)
Hb Constant Spring trait	3 (5.26)

Hb: hemoglobin

Sample size was estimated from a pilot study due to the absence of prior data. Using Stata version 16, with a proportion of anemia resolution of 0.43 in the abnormal Hb typing group, and 0.10 in the normal group, the level of significance (α) was 0.05, and a power of 0.8, at least 28 participants per group were required.

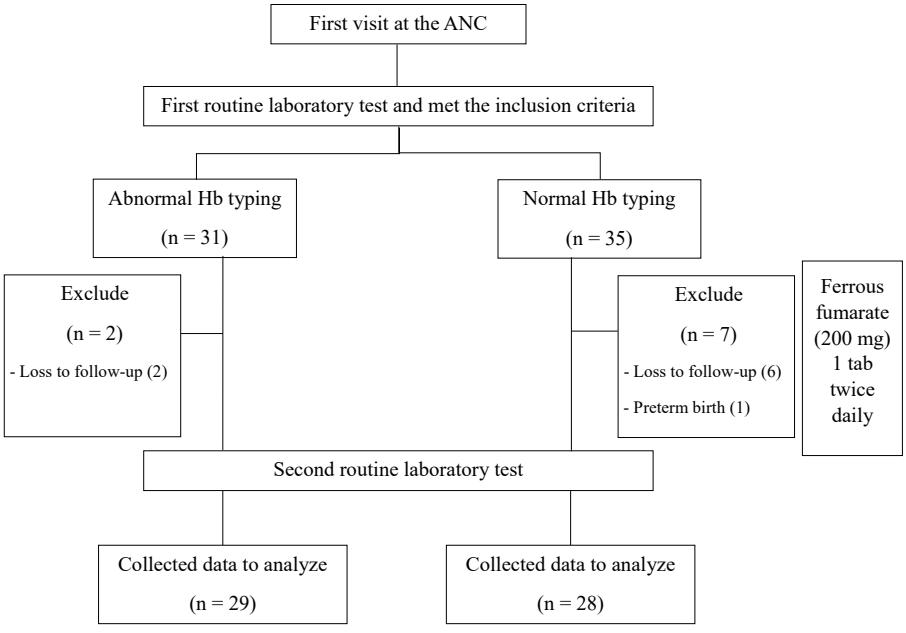

Fig. 1. Consort flow diagram.

ANC: antenatal care, Hb: hemoglobin

Stata version 16 was also used for statistical analysis. Quantitative data were presented as mean with standard deviation (SD) and compared using independent t-tests for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Qualitative data were presented as frequency and percentage and compared using chi-square test. Multilevel regression with random intercept and random slope was used to calculate changes in Hb levels between groups. A p value < 0.05 was considered statistically significant.

Results

Participants were recruited from October 2024 until the estimated sample size was reached in June 2025, with all laboratory results completed in August 2025. A total of 66 participants were enrolled: 31 in the abnormal Hb typing group, and 35 in the normal group. Two participants in the abnormal group were excluded due to loss to follow-up, and 6 participants in the normal group for the same reason and other women having preterm birth. No participants were excluded for intolerance to FF. Finally, 29 participants in the abnormal Hb typing group and 28 in the normal group were included in this analysis.

Baseline characteristics are presented in Table 2. The mean age was 24.76 ± 5.34 years in the abnormal Hb typing group and 25.39 ± 7.62 years in the normal group (p = 0.72). Most were of Thai nationality. Gravidity and parity were predominantly nulliparous. Iron supplementation was mostly initiated in the second trimester, with mean gestational age of 22.98 ± 6.50 weeks in the abnormal group and 22.24 ± 6.25 weeks in the normal group (p = 0.66). Duration of FF intake (28-128 days, 58.69 ± 26.30 days vs 61.39 ± 28.77 days) and compliance (94.89 ± 3.19 % vs 93.31 ± 4.33 %) were not significantly different between groups.

Table 2. Baseline characteristics.

Characteristic	Abnormal Hb typing (n = 29)	Normal Hb typing (n = 28)	p value
Maternal Age (years)	24.76 ± 5.34	25.39 ± 7.62	0.72
Nationality (n)			0.25
Thai	26 (89.66)	22 (78.57)	
Others	3 (10.34)	6 (21.43)	
Gravidity (n)			0.39
G 1	14 (48.28)	17 (60.71)	
G 2	8 (27.59)	8 (28.57)	
G ≥ 3	7 (24.14)	3 (10.71)	
Parity (n)			0.36
P 0	15 (51.72)	19 (67.86)	
P 1	8 (27.59)	7 (25.00)	
P 2	4 (13.79)	2 (7.14)	
P ≥ 3	2 (6.90)	0 (0)	
GA at start FF (n)			
1st trimester	0 (0)	1 (3.57)	0.30
2nd trimester	21 (72.41)	23 (82.14)	
3rd trimester	8 (27.59)	4 (14.29)	
Mean	22.98 ± 6.50	22.24 ± 6.25	0.66
Duration (days)	58.69 ± 26.30	61.39 ± 28.77	0.71
Compliance (%)	94.89 ± 3.19	93.31 ± 4.33	0.12

Hb: hemoglobin, SD: standard deviation, G: gravidity, P: parity, GA: gestational age, FF: ferrous fumarate
Data are presented as mean ± SD or n (%)
P values are from chi-square test or independent t-test

Table 3 presents laboratory findings related to anemia status. Hb levels at the first laboratory investigation, before iron supplementation, were not significantly different between the two groups (9.88 ± 0.66 g/dL in abnormal group and 9.85 ± 0.71 g/dL in normal group, p = 0.86). However, both the number of participants who achieved resolution of anemia and post-treatment Hb levels differed significantly. Resolution of anemia occurred in 8 participants (27.59%) in the abnormal Hb typing group compared with 20 participants (71.43%) in the normal group (p = 0.01). Mean Hb levels after iron supplementation were 10.37 ± 1.10 g/dL and 11.73 ± 1.19 g/dL in the abnormal and the normal group respectively (p < 0.001).

Table 3. Primary and secondary outcomes.

	Abnormal Hb typing (n = 29)	Normal Hb typing (n = 28)	p value
Anemia resolution (n) [A]	8 (27.59)	20 (71.43)	0.01
Hemoglobin level (g/dL)			
Before treatment	9.88 ± 0.66	9.85 ± 0.71	0.86
After treatment	10.37 ± 1.10	11.73 ± 1.19	< 0.001
Difference of change	0.49 ± 1.06	1.87 ± 1.46	< 0.001
Average per week	0.01 ± 0.02	0.11 ± 0.02	< 0.001
Number of Hb change (n)			
Increase level	19 (65.52)	27 (96.43)	0.003
Decrease level	10 (34.48)	1 (3.57)	0.003
Increase > 1 g/dL [B]	7 (24.14)	22 (78.57)	< 0.001
[A] and [B] (n)	6 (20.69)	20 (71.42)	< 0.001

Hb: hemoglobin, SD: standard Deviation, [A] and [B]: participants with anemia resolution and Hb increase > 1 g/dL
Data are presented as mean ± SD or n (%)
P values are from chi-square test or independent t-test

Average change in Hb levels per week also differed significantly between groups when analyzed with multilevel regression (0.01 ± 0.02 in the abnormal group versus 0.11 ± 0.02 in the normal group, p < 0.001). Fig. 2 shows individual Hb trends before and after iron supplementation, and Fig. 3 summarizes regression results. The normal group had a mean increase of 1.87 ± 1.46 g/dL compared with only a slight increase (0.49 ± 1.06 g/dL) in the abnormal group (p < 0.001), with some participants experiencing a decline in Hb levels.

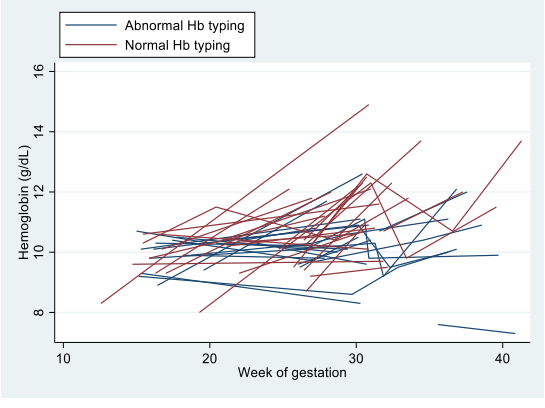

Fig. 2. Individual hemoglobin (Hb) trends before and after treatment in spaghetti plot
Y-axis: Hb level (g/dL); X-axis: gestational age (weeks).
Each line connects Hb at treatment initiation and at the end of follow-up.
Blue lines represent the abnormal Hb typing group.
Red lines represent the normal Hb typing group.

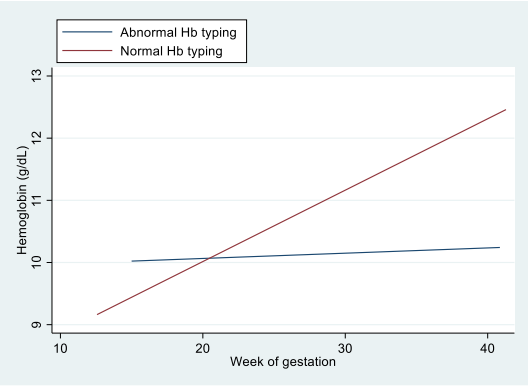

Fig. 3. Hb trends before and after treatment when summarizing after multilevel regression.
Y-axis: Hb level (g/dL); X-axis: gestational age (weeks).
Each line connects Hb at treatment initiation and at the end of follow-up.
Blue line represents the abnormal Hb typing group.
Red line represents the normal Hb typing group.

According to ACOG guideline, IDA may be diagnosed if Hb increases by more than 1 g/dL after treatment. Therefore, six participants in the abnormal Hb typing group whose anemia had been resolved could probably be diagnosed with coincident IDA. Two others improved despite not meeting this criterion; however, the sample size was too small to draw conclusions regarding the efficacy of iron supplementation in thalassemia trait. In contrast, all 20 participants in the normal group whose anemia had been resolved met the diagnostic criteria for IDA. This finding is consistent with the fact that IDA is the most common cause of anemia during pregnancy.

Discussion

Most participants in the abnormal Hb typing group did not achieve resolution of anemia, which was significantly different from the normal group. Moreover, some participants even showed a decrease in Hb levels after treatment, which may reflect other underlying causes of anemia or indicate that anemia associated with thalassemia trait does not respond to iron supplementation. This finding corresponded to the pathophysiology of anemia in thalassemia, which involves defective hemoglobin chain synthesis leading to ineffective erythropoiesis and hemolysis, rather than abnormalities in iron storage and metabolism as seen in iron deficiency anemia (IDA)[3, 8]. However, many variables that may influence Hb improvement were not examined in this study, and the thalassemia trait group may still benefit from iron supplementation depending on factors such as the duration, dosage, and route of iron administration, dietary intake, and the timing of administration.

This study's results were consistent with previous knowledge indicating that the most common cause of anemia in pregnancy is IDA, which can be corrected by iron supplementation[4, 5, 7, 11]. Strengths of this research include good compliance among participants and balanced baseline characteristics between the two groups. Participants represented the general local population, being Thai women of reproductive age. Furthermore, this study evaluated the outcomes of additional iron supplementation, rather than focusing solely on the prevalence of IDA and thalassemia as in previous studies[4, 5, 11, 12]. Finally, no participants were excluded because of intolerance to side effects of FF.

This study had some limitations and highlights

the need for further research. First, iron studies were not performed before additional supplementation, as this was a cohort study, and iron studies are not included as standard diagnostic tools in national guidelines for diagnosing anemia in pregnant women[10]. Second, although exclusion criteria were applied, some participants may have had other underlying causes of anemia. This was supported by the fact that some participants in the normal group did not achieve anemia resolution despite receiving an adequate dose and duration of iron supplementation. Therefore, this remained one of the study's limitations. Third, normal Hb typing results could not clearly differentiate α-thalassemia trait from non-thalassemia trait status, however, baseline Hb level and synthesis of Hb chains are nearly normal[8, 12]. On the other hand, individuals with abnormal Hb typing results consistent with disease forms were excluded because they would already be iron-overloaded. Thus, the "abnormal Hb typing" group would not include these women. Fourth, as a single-center study with a limited data collection period, the sample size was relatively small. The abnormal group can comprise various types of Hb abnormalities with different responses to iron supplementation and all cases might not be included in the study[12]. Future studies should address these limitations through randomized controlled trials with longer enrollment periods, as well as by exploring optimal dosage and methods to enhance iron absorption, such as administering intermittent iron supplementation e.g. three times per week[13, 14] or taking iron supplementation in the morning with ascorbic acid-rich foods[15].

Conclusion

The findings of this study showed differences in treatment response between anemic pregnant women with abnormal Hb typing, assumed to represent thalassemia trait, and those with normal Hb typing. While IDA can usually be corrected with additional iron supplementation, anemia caused by thalassemia cannot be resolved in exactly the same way.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Lidocaine Gel Combined with Ibuprofen Versus Ibuprofen Alone for Pain Relief during an Endometrial Biopsy; A randomized controlled trial

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ABSTRACT

Objectives: To study the effect of 2% lidocaine gel in conjunction with ibuprofen for pain relief during endometrial biopsy.

Materials and Methods: Women who met the eligibility criteria were randomly allocated into two groups. The intervention group received 2% lidocaine gel (3 mL), while the control group received the placebo gel (3 mL). Both groups received oral ibuprofen 400 mg 30 minutes before the procedure. The pain score in each step of the procedure, starting from speculum insertion, grasping the cervix, during endometrial biopsy, immediately after the procedure, and 10 minutes after the procedure, was assessed by a 10-cm visual analogue scale. Any adverse effects were also recorded.

Results: Eighty-six women, 43 in each group, were recruited during July to December 2024. Baseline characteristics, including age, parity, and menopausal status, were not different in both groups. The mean pain score during endometrial biopsy in the intervention group (3.30 ± 2.09) was significantly lower than in the control group (5.33 ± 2.01) (mean difference -2.03, 95% confidence interval -2.91 to -1.15, $p < 0.001$). Pain scores at each step of the procedure in the intervention group were lower than in the control group but not statistically different. Adverse effects were not found, and the satisfaction of both patients and physicians was satisfied.

Conclusion: The addition of 2% lidocaine gel was effective in reducing pain during endometrial biopsy when compared to ibuprofen alone.

Keywords: endometrial biopsy, lidocaine gel, ibuprofen, pain control.

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การศึกษาผลของยาลิโดเคนเจลร่วมกับยาแก้อักเสบไอบูโพรเฟนเทียบกับการให้ยาแก้อักเสบไอบูโพรเฟนเพียงอย่างเดียวในการลดอาการปวด ระหว่างการเก็บเยื่อบุโพรงมดลูก: การศึกษาแบบสุ่ม

เขมณัฏฐ์ ถือมั่น, ธัญญลักษณ์ วงศ์ลือชา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการใช้ยาลิโดเคนชนิดเจลร่วมกับการรับประทานยาแก้อักเสบไอบูโพรเฟนในการลดอาการปวด ระหว่างการเก็บเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุม โดยแบ่งกลุ่มสตรีที่มีเลือดออกจากช่องคลอดที่เข้าได้กับเกณฑ์ที่กำหนดเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยาลิโดเคนเจล (3 มล.) และกลุ่มได้รับยาหลอกชนิดเจล (3 มล.) โดยผู้เข้าร่วมวิจัยทั้งสองกลุ่มจะรับประทานยาแก้อักเสบ ไอบูโพรเฟน 400 มก.30 นาที และทาเจลบริเวณปากมดลูก 3 นาทีก่อนเริ่มทำหัตถการทั้งสองกลุ่ม และวัดระดับความเจ็บปวดโดยใช้มาตรวัด ความปวดตลอดการเก็บเยื่อบุโพรงมดลูก เริ่มตั้งแต่การใส่อุปกรณ์ถ่างช่องคลอด ขณะหนีบบริเวณปากมดลูก ในขณะทำหัตถการ และหลังจากทำ หัตถการเสร็จทันที และอีก 10 นาทีถัดมา โดยมีการติดตามอาการและอาการแสดงของภาวะไม่พึงประสงค์ตลอดการทำหัตถการ*

ผลการศึกษา: *จำนวนอาสาสมัครในงานวิจัยนี้มีทั้งสิ้น 86 คน แบ่งเป็นกลุ่มละ 43 คน เก็บข้อมูลระหว่างเดือนกรกฎาคม ถึง เดือนธันวาคม พ.ศ.2567 ข้อมูลพื้นฐานของผู้เข้าร่วม เช่นอายุ จำนวนบุตร และสถานะวัยหมดประจำเดือนไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างสองกลุ่ม ระดับความเจ็บปวดระหว่างการเก็บเยื่อบุโพรงมดลูกในกลุ่มที่ได้ยาลิโดเคนเจลคู่กับยาแก้อักเสบไอบูโพรเฟนน้อยว่ากลุ่มที่ได้ยาหลอกชนิดเจล ร่วมกับยาแก้อักเสบไอบูโพรเฟนอย่างมีนัยสำคัญ (3.30 ± 2.09 และ 5.33 ± 2.01 ตามลำดับ, ส่วนต่างเฉลี่ย -2.03, 95% confidence interval (-2.91-(-1.15)), $p < 0.001$) คะแนนความเจ็บปวดในแต่ละขั้นตอนของหัตถการมีแนวโน้มต่ำกว่าในกลุ่มทดลองแต่ยังไม่พบความแตกต่างกัน ทางนัยสถิติทั้งสองกลุ่มไม่พบอาการไม่พึงประสงค์จากการใช้ยาลิโดเคนเจล และระดับความพึงพอใจของผู้ป่วยอยู่ในเกณฑ์ดี*

สรุป: *การใช้ลิโดเคนเจลร้อยละ 2 ทาบริเวณปากมดลูก ร่วมกับไอบูโพรเฟนสามารถลดความเจ็บปวดระหว่างการเก็บเยื่อบุโพรงมดลูกได้อย่างมีประสิทธิผล เมื่อเทียบกับการใช้ไอบูโพรเฟนอย่างเดียว*

คำสำคัญ: *การเก็บเยื่อบุโพรงมดลูก, ลิโดเคนเจล, ไอบูโพรเฟน, การลดความเจ็บปวด*

Introduction

Abnormal uterine bleeding (AUB) is characterized by irregularity, excessive volume, altered frequency, or prolonged duration, occurring in the absence of pregnancy[1]. The etiologies of abnormal uterine bleeding are categorized by International Federation of Gynecology and Obstetrics and American College of Obstetricians and Gynecologists using the PALM-COEIN acronym, with endometrial cancer included among them[2]. The prevalence of endometrial cancer among premenopausal women with AUB was 10.5%[3]. Although one study found that only a subset of premenopausal women with AUB—those with obesity, tamoxifen use, or endometrial thickness greater than 10 mm—had a significantly increased risk for endometrial hyperplasia or carcinoma, with the risk markedly increased when more than one factor was present, this study had a low endometrial hyperplasia/endometrial cancer prevalence[4]. Thus, if they indicated an endometrial biopsy[5], they also required tissue to exclude malignancy.

The causes of abnormal uterine bleeding can be found using a variety of techniques, including endometrial biopsy and ultrasound, particularly transvaginal ultrasound, which is helpful for postmenopausal women. Endometrial biopsy plays a primary role in determining carcinoma, premalignant lesions, and other pathology-related bleeding. The endometrial biopsy can be performed using various office aspirators, hysteroscopy (either in-office or inpatient), or by fractional curettage, but currently the first line of treatment is an office endometrial biopsy[5].

Overall, high accuracy is achieved for diagnosing endometrial cancer when a sufficient sample is obtained using an endometrial biopsy, which has a sensitivity of 70.9% and a specificity of 97.2%[6]. One study found that endometrial biopsy had more sensitivity than fractional curettage for detecting high-grade malignancy, at 91.6% and 73.6%[3], respectively. And it has numerous advantages, including the fact that it can be performed as an outpatient procedure and rarely requires general anesthesia or intravenous sedation[7].

Endometrial biopsy is performed with endometrial suction devices, which are divided into low-pressure and high-pressure devices. In Khon Kaen Hospital, we have used the MedGyn Endosampler, a low-pressure device with a 3 mm curette and a 10-cc syringe, to reduce patients' discomfort. However, it can still cause moderate to severe pain during an endometrial biopsy, and pain is the most significant obstacle to the successful completion of the procedure[7].

The mechanism of pain during endometrial biopsy comes from two pathways: the first one from uterine cramping caused by inflammatory cytokines such as prostaglandins, and the second one from stimulation of the uterovaginal plexus, which supplies the lower part of the uterus and vagina. The cervix is the transitional zone between them; therefore, it has the most abundant nerve supply[8-12].

Several recent studies evaluated pain management during endometrial biopsy, including paracervical nerve block, non-steroidal anti-inflammatory drugs (NSAIDs), intrauterine lidocaine, and topical anesthetics such as lidocaine spray or gel applied to cervical areas[7]. However, a standard guideline for pain reduction during endometrial biopsy is still lacking, and the results are inconclusive.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are nonselective, reversible cyclooxygenase inhibitors, so they can inhibit prostaglandin synthesis. The onset of action of ibuprofen is 30–60 minutes, and the duration of analgesia is about 6–8 hours. Several studies had studied NSAIDs for relief of pain during the endometrial biopsy, but the results were inconclusive[8, 13].

A topical anesthetic agent like 2% lidocaine gel inhibits sodium influx into the cell membrane, thereby blocking the action potential of the peripheral nerve fibers so that pain can be reduced. The onset of action is short, as it begins after only about 3–5 minutes. Several studies have studied the analgesic effect of 2% lidocaine gel in endometrial biopsy [14-16], but the results have been inconclusive.

From the findings above, only one mechanism cannot reduce pain during endometrial biopsy. This research aimed to study the effect of 2% lidocaine gel in conjunction with ibuprofen for pain relief during endometrial biopsy.

Materials and Methods

From July to December 2024, this study was conducted as a double-blind, randomized, prospective, placebo-controlled trial. The participants were women who visited the Gynecology Outpatient Clinic at Khon Kaen Hospital in Khon Kaen, Thailand. The study has been registered at http://www.thaiclinicaltrials.gov (TCTR20240620003) in accordance with the standards established by the International Committee of Medical Journal Editors and the World Health Organization and has received approval from the Khon Kaen Hospital Institutional Review Board for Human Research (reference number: KEF67009).

The inclusion criteria were women ≥ 18 years old who had indicated endometrial biopsy: AUB in women aged 35 years or older, or women age < 35 years old with risk factors including a history of unopposed estrogen exposure, failed medical management, or persistent AUB; and other indications including AUB in women taking tamoxifen or postmenopausal bleeding. The exclusion criteria were a history of lidocaine allergy, previous history of NSAIDs allergy, history of gastric ulcer, gastritis or gastrointestinal bleeding, asthma, uncontrolled hypertension, bleeding disorders, kidney disease, liver disease, glucose-6-phosphate dehydrogenase deficiency, cardiac arrhythmias, coronary heart disease, uterine anomaly, or massive vaginal bleeding, receiving misoprostol for cervical dilation, cervical stenosis, ongoing vaginal, cervix or pelvic infection, combination with endocervical biopsy, inability to pass an instrument into the endometrial cavity, inability to provide consent or participate in postoperative evaluation due to dementia, cognitive impairment or language barrier, and inability to use the visual analogue scale (VAS). Informed consent was obtained from all participants before conducting the procedure.

Participants were randomly assigned to one of two groups: 2% lidocaine gel with ibuprofen (intervention group) or placebo gel with ibuprofen (control group), by a computer-generated random number sequence using a block of four. A pharmacist, who was not involved in the study, prepared the study medications under sterile conditions. The 2% lidocaine gel and the placebo gel (a water-based hydroxyethyl-cellulose gel [Q-C, I.T.O. Chemical (1979) LTD.] with other excipients per manufacturer) were packaged in identical 3 mL syringes. The procedures were performed by trained gynecology residents or attending gynecologists from the Obstetrics and Gynecology Department at Khon Kaen Hospital. Participants were instructed to rate their pain level on a 10-cm VAS. Pain scores were recorded by drawing a line at each step of the procedure and collected by the first nursing assistant, who was not involved in performing the procedure or in the randomization process.

Before the procedure, all the participants received an identical protocol, which included a pelvic examination and a pelvic ultrasound performed by a gynecologist to determine endometrial thickness; those who met the eligibility criteria were randomly assigned. Allocation concealment was maintained by using seals and opaque envelopes. Patients, operators, and pain recorders were all blinded.

The opaque envelopes were opened by the second nursing assistant, who was not involved in

outcome assessment. The envelopes contained the unnamed solution (either 2% lidocaine gel or placebo gel), sealed in an opaque medication envelope, along with ibuprofen.

All participants in both groups received 400 mg of oral ibuprofen 30 minutes before the procedure. Endometrial biopsy was performed using a MedGyn Endosample, with a semi-rigid cannula with a 3 mm diameter and a 10-cc syringe as the catheter device. Thirty minutes later, participants were placed in the lithotomy position for the procedure. The speculum was placed into the vagina to identify the cervix; the pain score (P0) was recorded at this time as the baseline pain score. The vagina and cervix were sterilized with a povidone-iodine solution.

Participants in the intervention group received 3 mL of 2% lidocaine gel applied to the anterior and posterior cervical surfaces using a wooden Ayre spatula. In comparison, those in the control group received 3 mL of placebo gel applied in the same manner. Applications were performed by gynecology residents or attending staff who were not otherwise involved in the study. After waiting three minutes for the onset of the analgesic effects, the anterior lip of the cervix was grasped with the tenaculum to track the uterus, and the pain score was assessed using the VAS at this time point (P1). The uterine sound was inserted into the uterine cavity to record the depth of the uterus, followed by insertion of the MedGyn endosampler. An endometrial biopsy was done by a corkscrew twisting technique and aspiration curettage; the pain score was assessed using the VAS during endometrial biopsy (P2). After the removal of all equipment, the pain score was evaluated using the VAS immediately (P3). The participants' vital signs, as well as the adverse effects associated with lidocaine gel, such as palpitation, hypotension, dyspnea, drowsiness, and signs of uterine perforation such as severe pelvic pain, were monitored until ten minutes after the procedure, and the pain score was assessed again with the VAS (P4).

All primary and secondary outcomes were recorded. The primary outcome was the pain score during endometrial biopsy (P2). The secondary outcomes were the pain score during speculum insertion (P0), during the grasping of the cervix with the tenaculum (P1), immediately after the removal of all equipment (P3), and at ten minutes after the procedure (P4), as well as the satisfaction score of the patients with the pain, the satisfaction score of the physicians with the smoothness, histological findings, additional anesthesia, and the side effects of lidocaine gel.

The study was based on a pilot study involving 30 participants; each group consisted of 15 women. The mean pain score during endometrial biopsy in the intervention group was 3.36 with a standard deviation (SD) of 2.05, while in the control group the mean pain score during endometrial biopsy was 4.86 with a SD of 1.99. With a power of 90%, a significance level of 0.05, and a dropout rate of 10%, the sample size was calculated, and the study required a total population of 86 participants, with 43 in each group. Randomization was performed using a computer-generated random number sequence, using a block of four.

The data were analyzed using SPSS version 18 based on an intention-to-treat analysis. Continuous data were analyzed using the student's t-test for normally distributed data or the Mann-Whitney U test for data that was not normally distributed and were presented as descriptive statistics (mean ± SD or median ± interquartile range, as appropriate). Categorical data were analyzed by the chi-square test or Fisher's exact test if the expected count was less than five and presented as count number and percentage (n, %). The difference in pain scores between the two groups was compared using analysis of longitudinal data (linear mixed-effects model). Statistical significance was determined as a p value less than 0.05.

Results

Between July and December 2024, all 86 eligible women had indications for an endometrial biopsy; no one was excluded. The 86 cases were randomly assigned: 43 to the 2% lidocaine gel with ibuprofen group (intervention group) and 43 to the placebo gel with ibuprofen group (control group). There were no dropouts (Fig. 1).

Baseline characteristics were comparable between groups (Table 1). The mean age was 47.8 ± 7.9 years in the intervention group and 46.6 ± 6.9 years in the control group. AUB was the most common indication for biopsy.

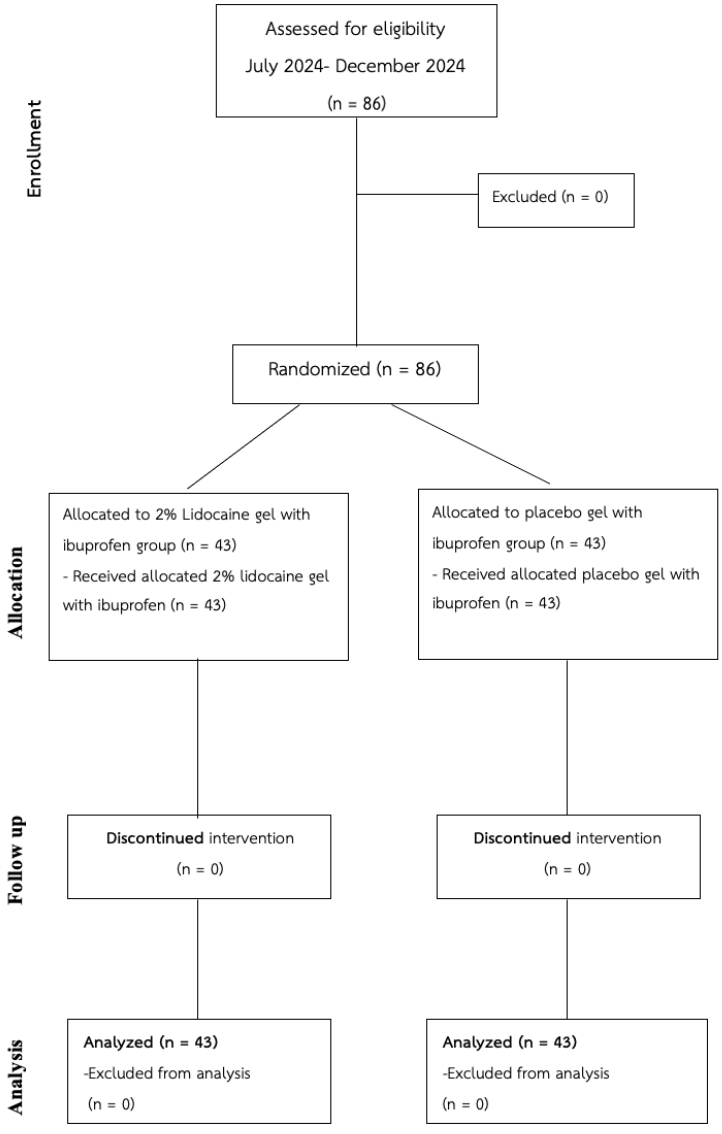

Fig. 1. Study flow.

Table 1. Baseline characteristics.

	Intervention group (n = 43)	Control group (n = 43)	p value
Age (years), mean ± SD	47.8 ± 7.9	46.6 ± 6.9	0.395[a]
BMI (kg/m^2), mean ± SD	26.4 ± 4.8	26.8 ± 5.3	0.711[a]
Underlying disease, n (%)			0.063[b]
Yes	9 (20.9)	18 (41.9)	
DM	3 (7.0)	3 (7.0)	
Hypertension	5 (11.6)	7 (16.3)	
Others			
- Hyperthyroid	2 (4.7)	1 (2.3)	
- Allergic Rhinitis	0 (0.0)	1 (2.3)	
- Autoimmune disease	1 (2.3)	3 (7.0)	
- Breast Cancer	0 (0.0)	3 (7.0)	
No	34 (79.1)	25 (58.1)	
Parity, n (%)			0.518[b]
Nulliparous	4 (9.3)	7 (16.3)	
Multiparous	39 (90.7)	36 (83.7)	
Menopausal status, n (%)			0.298[b]
Premenopausal	31 (72.1)	36 (83.7)	
Postmenopausal	12 (27.9)	7 (16.3)	
Previous vaginal delivery, n (%)			0.518[c]
Yes	39 (90.7)	36 (83.7)	
No	4 (9.3)	7 (16.3)	
Previous procedure at cervix or uterus, n (%)			0.770[b]
Yes	6 (14.0)	8 (18.6)	
- Endometrial biopsy	1 (2.3)	5 (11.6)	
- Curettage	4 (9.3)	1 (2.3)	
- Manual vacuum aspiration	1 (2.3)	1 (2.3)	
- Cervical biopsy	2 (4.6)	1 (2.3)	
- Intrauterine device insertion	0 (0.0)	1 (2.3)	
No	37 (86.0)	35 (81.4)	
Indication for endometrial sampling, n (%)			
Abnormal uterine bleeding	29 (67.4)	35 (84.1)	0.217[b]
Postmenopausal bleeding	13 (30.2)	7 (16.3)	0.202[b]
Endometrial hyperplasia	1 (2.3)	1 (2.3)	1.000[c]
Gynecologic disease, n (%)			0.666[b]
Yes	21 (48.8)	24 (55.8)	
Adenomyosis	6 (14)	11 (25.6)	
Myoma uteri	16 (37.2)	13 (30.2)	
Others			
Endometrial Hyperplasia	1 (2.3)	0 (0.0)	
Endometriosis	1 (2.3)	0 (0.0)	
No	22 (51.2)	19 (44.2)	
Endometrial thickness (cm.), median (IQR)	0.4 (0.3,0.7)	0.5 (0.3,0.8)	0.193[d]
Depth of uterus (cm.) median (IQR)	8 (7,9.5)	7 (7,9)	0.403[d]

[a] student's t-test, [b] chi-square, [c] Fisher's exact test, [d] Mann-Whitney U test
BMI: body mass index, SD: standard deviation, IQR: interquartile range

There was no difference in baseline pain scores between the intervention group (1.04 ± 1.43) and the control group (1.13 ± 1.48) (mean difference -0.09, p = 0.779) (Table 2). When compared with the baseline pain score, the mean pain score at each procedural step is presented in Table 3 and Fig. 2. During endometrial biopsy, the mean change in pain score was significantly lower in the intervention group (2.26, 95%CI 1.69-2.83) compared with the control group (4.21, 95%CI 3.64-4.78), with a mean difference of 1.95 (95%CI 1.14-2.76, p < 0.001). The intervention group consistently showed lower mean change in pain scores than the control group during tenaculum grasping, device insertion, immediately post-procedure, and ten minutes post-procedure; these differences did not reach statistical significance.

Table 2. Pain score in each step of endometrial sampling procedure.

VAS pain score, mean ± SD	Intervention group (n = 43)	Control group (n = 43)	Mean difference (95%CI)	p value
Speculum insertion (P0)	1.04 ± 1.43	1.13 ± 1.48	- 0.09 (-0.71-0.53)	0.779
Grasping tenaculum (P1)	2.16 ± 1.86	2.81 ± 2.14	- 0.65 (-1.51-0.21)	0.137
During endometrial biopsy (P2)	3.30 ± 2.09	5.33 ± 2.01	-2.03 (-2.91-(-1.15))	< 0.001
Immediately after procedure (P3)	2.21 ± 1.92	3.03 ± 2.26	- 0.83 (-1.72-0.07)	0.077
10 minutes after procedure (P4)	0.68 ± 0.95	1.13 ± 1.56	-0.46 (-1.00-0.10)	0.109

SD: standard deviation, CI: confidence interval

Table 3. Mean pain score compared with baseline

Pain score	Intervention group (n = 43) mean change (95%CI)	p value	Control group (n = 43) mean change (95%CI)	p value	Different mean change (95%CI)	p value
Grasping tenaculum (P1)	1.12 (0.55-1.69)	< 0.001	1.68 (1.11-2.25)	< 0.001	0.56 (-0.25-1.37)	0.176[e]
During endometrial biopsy (P2)	2.26 (1.69-2.83)	< 0.001	4.21 (3.64-4.78)	< 0.001	1.95 (1.14-2.76)	< 0.001[e]
Immediately after procedure (P3)	2.17 (0.60-1.74)	< 0.001	1.87 (1.30-2.45)	< 0.001	0.71 (-0.10-1.52)	0.088[e]
10 minutes after procedure (P4)	-0.36 (-0.93-0.21)	0.221	0.01 (-0.57-0.58)	0.988	0.36 (-0.45-1.17)	0.380[e]

[e] linear mixed-effects model
CI: confidence interval

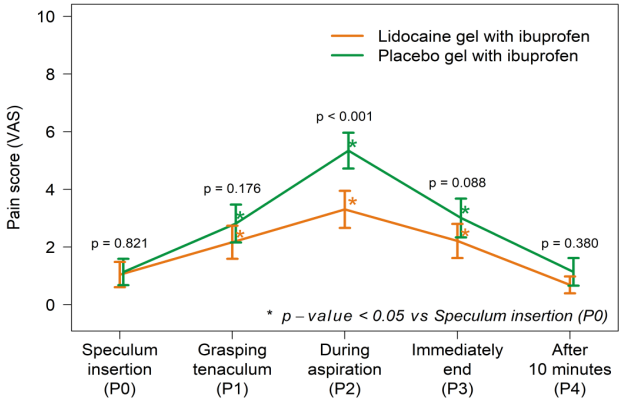

Fig. 2. A Linear mixed-effects model of mean change pain score during each step of endometrial biopsy.

VAS: visual analogue scale

No participants required additional analgesic, and no adverse effects related to lidocaine or the procedure were observed in this study. Both patient and physician satisfactions were high in both groups, with the majority reporting complete satisfaction. Histopathological findings of the endometrial samples did not differ significantly between the groups, with proliferative endometrium being the most common result (Table 4, 5).

Table 4. Other secondary outcomes.

	Intervention group (n = 43)	Control group (n = 43)	p value
Satisfaction of patient, n (%)			0.233[c]
Completely satisfied	38 (88.4)	32 (74.4)	
Satisfied	3 (7.0)	8 (18.6)	
No idea	2 (4.7)	3 (7.0)	
Dissatisfied	0 (0.0)	0 (0.0)	
Completely dissatisfied	0 (0.0)	0 (0.0)	
Satisfaction of physician, n (%)			0.228[c]
Completely satisfied	39 (90.7)	34 (79.1)	
Satisfied	4 (9.3)	8 (18.6)	
No idea	0 (0.0)	1 (2.3)	
Dissatisfied	0 (0.0)	0 (0.0)	
Completely dissatisfied	0 (0.0)	0 (0.0)	

[c] Fisher's exact test

Table 5. Histopathological findings.

	Intervention group (n = 43)	Control group (n = 43)	p value
Pathological findings, n (%)			
Proliferative endometrium	18 (41.9)	24 (55.8)	0.281b
Secretory endometrium	7 (16.3)	2 (4.7)	0.156c
Endometrial cancer	1 (2.3)	2 (4.7)	1.000c
Others			
- Acute endometritis	1 (2.3)	0 (0.0)	1.000c
- Benign endometrial tissue	3 (7.0)	3 (7.0)	1.000c
- Chronic endometritis	3 (7.0)	2 (4.7)	1.000c
- Endometrial polyp	2 (4.7)	3 (7.0)	1.000c
- Glandular and stromal breakdown	4 (9.3)	2 (4.7)	0.676c
- High grade squamous intraepithelial lesion (CIN3)	1 (2.3)	0 (0.0)	1.000c
- Inactive endometrium	0 (0.0)	2 (4.7)	0.494c
- Inaccessible simple	1 (2.3)	1 (2.3)	1.000c
- Necrotic tissue	1 (2.3)	0 (0.0)	1.000c
- Progestational effect	1 (2.3)	2 (4.7)	1.000c

[b] chi-square; [c] Fisher's exact test
CIN: cervical intraepithelial neoplasia

Discussion

Because AUB is a common condition in about 14-25% of reproductive-age women[17] and malignancy is found in around 5.3%[18], identifying the causes of AUB in high-risk women is essential. Currently, office endometrial biopsy stands as the first-line diagnostic method. However, a significant barrier to the successful execution of this procedure is pain perception[7].

The baseline pain score did not differ between the intervention group (1.04 ± 1.43) and the control group (1.13 ± 1.48). No statistically significant difference in pain scores was seen during tenaculum grasping, device insertion, immediately post-procedure, and ten minutes post-procedure between the intervention and the control groups. The highest pain scores occurred during the aspiration phase. Although the pain scores during speculum insertion, grasping of the cervix, immediately post-procedure, and ten minutes post-procedure were lower in the intervention group than in the control group, the difference was not statistically significant.

A significant reduction in pain was found only during the aspiration step. While the mean difference of approximately 2 cm on the VAS may not reach the threshold for clinical significance, the shift from moderate to mild pain may still be meaningful for patient comfort, particularly in outpatient gynecologic settings.

Evidence from previous studies supports the use of multimodal analgesia. Unlu et al[19] demonstrated that paracervical cream combined with NSAIDs or intrauterine lidocaine with NSAIDs significantly reduced pain during hysterosalpingography compared with single-agent regimens. Their findings aligned with our study, in which the combined use of topical anesthetic and NSAIDs resulted in the lowest pain scores. Similarly, Dogan et al[20] reported that intrauterine lidocaine with NSAIDs was superior to single-agent analgesia during endometrial biopsy.

Studies using single analgesic agents have yielded mixed results. Karaca et al[14] and Likkasittipan et al[16] found that cervical application of 2% lidocaine gel reduced pain during biopsy, whereas Kozman et al[15] reported no benefit. Similarly, other topical local anesthetic agent, such as lidocaine spray assessed by Sripha et al[21] and by Korsuwan et al[22], also showed inconsistent effects. NSAID-only regimens have variable outcomes: Tanprasertkul et al[8] found no significant benefit with etoricoxib, whereas Somchit et al[13] found that naproxen significantly reduced pain. A systematic review and meta-analysis by Charoenkwan et al[7] examined various methods of pain control including NSAIDs, paracervical block, intrauterine lidocaine, and topical anesthetics, but concluded that evidence remains inconclusive. Our findings support the concept that single-agent analgesia may be insufficient because pain from endometrial biopsy results from both inflammatory and cervical nerve pathways[8–12]. Combining NSAIDs, which reduce prostaglandin-mediated inflammation, with local cervical anesthesia may therefore provide more comprehensive analgesia. The pain scores of the intervention group and the control group during speculum insertion or tenaculum grasping were not statistically significantly different, consistent with the results of a prior study[14]. The pain scores immediately after the procedure (P3) and ten minutes afterward (P4) in the intervention group and the control group were not significantly different, as ibuprofen has an analgesic duration of approximately 6–8 hours and 2% lidocaine gel has a duration of local analgesia of 30 minutes to 12 hours or more.

Furthermore, no adverse events resulted from the lidocaine gel or the procedure reported, and both the patients and physicians expressed complete satisfaction with this study.

In an outpatient setting, lidocaine gel applied to the cervix in conjunction with oral ibuprofen could reduce pain during endometrial biopsy. Additionally, lidocaine gel and ibuprofen are readily available in hospitals, and preparation is uncomplicated. This should be considered by physicians for their clinical practice.

Strengths of this study included its prospective, double-blind, randomized, placebo-controlled design with adequate statistical power and no loss to follow-up. Pain was assessed at multiple time points, allowing for dynamic evaluation and appropriate repeated-measures analysis using a linear mixed-effects model. Additionally, the multimodal analgesic regimen was easy to administer and suitable for outpatient settings.

However, several limitations should be acknowledged. This was a single-center study, limiting generalizability. Pain was assessed using the VAS, a subjective but validated measure[23, 24]. Future studies should explore the lowest effective doses of lidocaine gel and ibuprofen, evaluate their use in more challenging populations such as nulliparous or postmenopausal women[25], and include multicenter trials comparing various analgesic techniques.

Conclusion

The combination of analgesic drugs with 2% lidocaine gel and ibuprofen showed effectiveness for relieving pain during endometrial biopsy compared to ibuprofen alone without any serious adverse events, supporting its use in routine clinical practice.

Acknowledgements

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Maternal Factors Associated with Early Onset Neonatal Sepsis in Preterm newborns at Maharat Nakhon Ratchasima Hospital

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ABSTRACT

Objective: To investigate maternal factors associated with early-onset neonatal sepsis in preterm infants at Maharat Nakhon Ratchasima Hospital.

Materials and Methods: This retrospective case-control study included singleton preterm neonates born at Maharat Nakhon Ratchasima Hospital between gestational ages of 24–36^{+6} weeks, from 2021 to 2023, totaling 497 cases. The study population consisted of 166 preterm neonates diagnosed with early-onset neonatal sepsis (EONS) and 331 preterm neonates without sepsis (case-control ratio 1: 2). Maternal demographic and clinical data were obtained from medical records. Descriptive statistics summarized baseline characteristics, while multiple logistic regression model identified maternal factors associated with EONS. Associations were reported as odds ratio (OR) with 95% confidence intervals (CI), with $p < 0.05$ considered statistically significant.

Results: Maternal factors significantly associated with EONS included gestational age less than 34 weeks (OR 2.77, 95%CI 1.74–4.40, $p < 0.001$), chorioamnionitis (OR 3.33, 95%CI 1.21–9.17, $p = 0.02$), maternal white blood cell count greater than 15,000 cells/μL (OR 1.92, 95%CI 1.16–3.20, $p = 0.012$).

Conclusion: Gestational age < 34 weeks, maternal chorioamnionitis, and maternal leukocytosis were significant risk factors associated with EONS in preterm neonates. Awareness of these factors may help in early recognition and clinical management.

Keywords: preterm neonates, early-onset neonatal sepsis, risk factors, chorioamnionitis.

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ปัจจัยของมารดาที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดในทารกคลอดก่อนกำหนดในโรงพยาบาลมหาราชนครราชสีมา

จิดาภา เอี่ยมเจริญลาภ, ฐิตินันท์ สมุทรไชยกิจ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาปัจจัยของมารดาที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดในทารกคลอดก่อนกำหนดในโรงพยาบาลมหาราชนครราชสีมา*

วัสดุและวิธีการ: *การศึกษาแบบวิเคราะห์แบบย้อนหลัง (Retrospective case-control study) ทำการศึกษาในทารกครรภ์เดี่ยวคลอดก่อนกำหนด เกิดในโรงพยาบาลมหาราชนครราชสีมา อายุครรภ์ระหว่าง 24–36^{+6} สัปดาห์ จำนวน 497 ราย ที่เกิดในช่วงปี พ.ศ. 2564 ถึงปี พ.ศ. 2566 โดยกลุ่มประชากร ได้แก่ ทารกคลอดก่อนกำหนดที่มีภาวะการติดเชื้อแรกเกิด จำนวน 166 คน และ ทารกคลอดก่อนกำหนดที่ไม่มีภาวะติดเชื้อแรกเกิด จำนวน 331 คน (อัตราส่วน 1 ต่อ 2) ข้อมูลประชากรและข้อมูลทางคลินิกของมารดาได้จากเวชระเบียน โดยใช้สถิติเชิงพรรณนาเพื่อสรุปลักษณะพื้นฐานของกลุ่มตัวอย่าง และใช้การวิเคราะห์ถดถอยโลจิสติกแบบพหุ เพื่อศึกษาปัจจัยของมารดาที่สัมพันธ์กับภาวะติดเชื้อในทารกแรกเกิดในทารกคลอดก่อนกำหนด รายงานค่า odds ratio (OR) และ 95% confidence interval (CI) โดย p value < 0.05 ถือว่ามีนัยสำคัญทางสถิติ*

ผลการศึกษา: *ปัจจัยที่สัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิด อย่างมีนัยสำคัญทางสถิติ ได้แก่ อายุครรภ์ที่น้อยกว่า 34 สัปดาห์ (OR 2.77, 95%CI 1.74-4.40, p < 0.001) ภาวะการติดเชื้อในถุงน้ำคร่ำ (OR 3.33, 95%CI 1.21 -9.17, p = 0.02) และระดับเม็ดเลือดขาวของมารดาที่มากกว่า 15,000 เซลล์/ไมโครลิตร (OR 1.92, 95%CI 1.16-3.20, p = 0.012)*

สรุป: *อายุครรภ์ที่น้อยกว่า 34 สัปดาห์, ภาวะติดเชื้อในถุงน้ำคร่ำ, และระดับเม็ดเลือดขาวของมารดาที่มากกว่า 15,000 เซลล์/ไมโครลิตรสัมพันธ์กับการเกิดภาวะติดเชื้อแรกเกิดของทารกคลอดก่อนกำหนด การตระหนักถึงปัจจัยเหล่านี้อาจช่วยในการวินิจฉัยภาวะติดเชื้อแรกเกิดได้ตั้งแต่ระยะเริ่มต้นและให้การดูแลรักษาที่เหมาะสมในทารกคลอดก่อนกำหนด*

คำสำคัญ: *ทารกคลอดก่อนกำหนด, ภาวะการติดเชื้อแรกเกิด, ปัจจัยเสี่ยง, ภาวะการติดเชื้อในถุงน้ำคร่ำ*

Introduction

Preterm birth is a common health problem and is the major cause of neonatal morbidity and disability. One of the primary contributors to mortality among preterm neonates is early-onset neonatal sepsis (EONS). According to the World Health Organization (WHO), approximately 13.4 million babies were born prematurely in 2020, accounting for 9.9% of all live births, or about 1 in every 10 births. In 2021, nearly one million preterm infants died before the age of five due to complications related to prematurity.[1]

In Thailand, data from the Ministry of Public Health in 2023 reported a preterm birth rate of 10.4%. According to the previous study, the incidence of preterm birth in Northeast Thailand was 10.83%.[2] In Nakhon Ratchasima province, the rate was 8.96%, while at Maharat Nakhon Ratchasima Hospital, the rate was as high as 11.96%, which is higher than the average due to referrals from surrounding hospitals. Over the period of 2000-2013 in 194 countries, the leading causes of neonatal death in the early neonatal period (age 0-6 days) were prematurity (40%), intrapartum complication (27%), and neonatal infections (8%).[3] Preterm birth affects mothers of all ages. A study conducted at Charoenkrung Pracharak Hospital found that teenage pregnancies have a notably higher rate of preterm delivery, especially in young adolescents.[4]

Early onset neonatal sepsis (EONS) is defined as a bloodstream infection occurring within the first 72 hours after birth, which is common and is a leading cause of death in neonates. As reported by a 2020 systematic review published in Global Child Health, the incidence of EONS between 2009 and 2018 was 3,112 cases per 100,000 live births, increasing to over to 10,000 cases per 100,000 live births among preterm neonates.[5] The pathogenesis of preterm EONS is primarily associated with intra-amniotic infection, which typically begins prior to the onset of labor and contributes to preterm labor or premature rupture of membranes (PROM). Microbial-induced maternal inflammation may trigger the initiation of parturition and provoke fetal inflammatory responses, ultimately leading to neonatal sepsis.[6]

Multiple maternal factors have been identified as potential contributors to EONS, including advanced maternal age (> 35 years), gestational age < 34weeks, obesity, excessive gestational weight gain, preterm premature rupture of membranes (PPROM), intrapartum fever, chorioamnionitis, maternal leukocytosis (> 15,000 cells/μL), and elevated neutrophil-to-lymphocyte ratio (NLR) > 5.[7-12] However, the independent effects of these factors remain inconsistent across populations, particularly in our country.

Preterm birth is high risk for EONS and is associated with high mortality rates. Given the higher-than-average preterm birth rates at our institution and the clinical burden of EONS among these vulnerable neonates, identifying maternal predictors is essential for improving early detection and targeted interventions. Therefore, this study aimed to investigate maternal factors associated with EONS in preterm infants (within 72 hours after birth) at Maharat Nakhon Ratchasima Hospital, a tertiary referral center in northeastern Thailand. The findings of this study could provide useful statistical data to enhance screening and risk-based clinical care for mothers at risk for preterm birth.

Material and Methods

This retrospective case-control study was conducted after approval from the Human Research Ethics Committee of Maharat Nakhon Ratchasima Hospital (MNRH IRB) and issued certificate number 126/2024. This study aimed to identify maternal factors associated with EONS in preterm neonates. The study was conducted on 497 preterm neonates who were born from January 2021 to December 2023 at Maharat Nakhon Ratchasima Hospital.

Eligible participants were singleton preterm neonates born at 24–36^{+6} weeks' gestation. Neonates with incomplete medical records, congenital anomalies, or indicated preterm births were excluded. The diagnosis of EONS, as defined by the American Academy of Pediatrics, requires a positive blood or

cerebrospinal fluid culture and/or clinical signs consistent with sepsis, supported by abnormal laboratory findings. Clinical signs may include (1) abnormal body temperature (> 37.5°C or < 36°C), (2) heart rate abnormalities (< 100 or > 180 beats per minute) or delayed capillary refill (> 3 seconds) or hypotension below age-specific thresholds, (3) respiratory rate > 60 breaths/min, or signs of respiratory distress such as grunting, chest retractions, or PaO_2 < 70 mmHg, (4) circulatory abnormalities (e.g., altered consciousness, oliguria, or venous blood pH < 7.25), (5) gastrointestinal symptoms (e.g., poor feeding, feeding intolerance, or abdominal distension), and (6) general symptoms such as irritability, lethargy, or hypotonia.[13] Laboratory criteria supporting the diagnosis include an (1) immature-to-total neutrophil (I/T) ratio ≥ 0.2 or neutropenia, (2) platelet count < 150,000 cells/mm^3, and (3) C-reactive protein (CRP) > 5 mg/L after 6 hours of life.[14]

A pilot study of 50 cases informed the planning of this study. For clarity and clinical relevance, gestational age at delivery < 34 weeks, which has been consistently associated with an increased risk of EONS,[8] was selected as the main factor for the sample size justification in this study with proportions of 0.417 in cases (P_1) and 0.579 in controls (P_2). Assuming α = 0.05, power = 0.80, a 2:1 control-to-case ratio, and adjustment for other explanatory variables ($R^2 \approx 0.24$), the minimum required sample size was 164 cases and 327 controls (total = 491 neonates). For analysis, two controls per case were randomly selected from the study population during the same period (unmatched 1: 2 design) using computer-generated random numbers independent of exposure. The final dataset comprised 166 cases and 331 controls (total = 497 neonates).

Maternal demographic, obstetric, and clinical data, including antepartum, intrapartum, mode of delivery, treatment, laboratory (latest laboratory results within 72 hours prior to delivery) and neonatal outcomes, were extracted from medical records.

Descriptive statistics (mean, standard deviation, median, interquartile range, and percentage) summarized baseline characteristics. Multiple logistic regression was used to assess maternal factors associated with EONS. Variables included in the multivariable model were maternal age, excessive gestational weight gain, PPROM, gestational age < 34 weeks, chorioamnionitis, maternal NLR ≥ 5, and maternal white blood cell count (WBC) > 15,000/μL. Selection was based on clinical relevance and prior evidence. A full-model strategy was applied, retaining all variables of theoretical or clinical importance regardless of statistical significance. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), and p values < 0.05 were considered statistically significant.

Results

A total of 497 preterm neonates at Maharat Nakhon Ratchasima Hospital were included in this study, which comprised 166 cases with EONS and 331 cases without EONS. Maternal characteristics and pregnancy outcomes are shown in Table 1. For maternal factors, statistically significant differences were observed between the two groups, including PPROM (46.4% vs 53.8%, p = 0.001), maternal fever (10.8% vs 4.8%, p = 0.022), chorioamnionitis (9.0% vs 1.8%, p < 0.001), antenatal dexamethasone used (61.4% vs 42.9%, p = 0.002), and maternal diabetes (15.6% vs 9.6%, p = 0.049).

EONS neonates were more frequently born before 34 weeks' gestation (58.4% vs 32.6%, p < 0.001) and had a higher rate of very low birth weight (< 1,500 g) (19.9% vs 9.7%, p = 0.001), while non-EONS neonates more often weighed 2,500–4,000 g (33.5% vs 22.3%). Low Apgar scores (< 7) were more common in the EONS group at both 1 minute (25.3% vs 10.3%) and 5 minutes (12.1% vs 2.7%) (p < 0.001 for both). Furthermore, Neonatal intensive care unit admissions were also significantly higher among the EONS group (30.7% vs 9.4%, p < 0.001).

Mothers of neonates with EONS exhibited significantly higher WBC counts compared to mothers of non-EONS neonates (mean 13,749 ± 5,087 vs 12,366 ± 3,718 cells/μL, p = 0.001). Additionally, the

NLR was significantly elevated in the EONS group [median 6.6 (IQR 3.6–10.5) vs 5.2 (IQR 3.6–7.9), p = 0.022]. The lymphocyte percentage was lower in the EONS group (13.9% ± 7.3 vs 15.2% ± 6.4, p = 0.034). No significant differences were observed between groups in other hematologic parameters, including hemoglobin, hematocrit, and platelet counts (Table 2).

Table 1. Maternal characteristics and pregnancy outcomes between two groups.

Characteristics	Early onset neonatal sepsis, n = 166	Non-early onset neonatal sepsis, n = 331	p value
Maternal age (years), mean ± SD	28.0 ± 6.92	27.1 ± 6.73	0.347
Antenatal care visit			0.254
< 8 times	87 (52.4)	155 (46.8)	
≥ 8 times	79 (47.6)	176 (53.2)	
Maternal BMI (kg/m^2), mean ± SD	23.8 ± 6.13	22.7 ± 5.29	0.328
Excessive gestational weight gain	137 (82.5)	267 (80.7)	0.715
Nulliparous	74 (44.6)	172 (52.0)	0.129
PPROM			0.001*
No PPROM	89 (53.6)	153 (46.2)	
≤ 18 hours	34 (20.5)	118 (35.7)	
> 18 hours	43 (25.9)	60 (18.1)	
Maternal fever	18 (10.8)	16 (4.8)	0.022*
Maternal UTI	14 (8.4)	20 (6.0)	0.348
Chorioamnionitis	15 (9.0)	6 (1.8)	< 0.001*
Antenatal dexamethasone used	102 (61.4)	142 (42.9)	0.002*
Antenatal antibiotics used	135 (81.3)	256 (77.3)	0.353
Route of delivery			0.490
Vaginal route	94 (56.6)	187 (56.5)	
Cesarean section	72 (43.4)	144 (43.5)	
Maternal Diabetes			0.049*
Overt DM	5 (3.0)	5 (1.5)	
GDMA1	10 (6.0)	20 (6.0)	
GDMA2	11 (6.6)	7 (2.1)	
Gestational age at delivery			< 0.001*
< 34 weeks	97 (58.4)	108 (32.6)	
34-36^{+6} weeks	69 (41.6)	223 (67.4)	
Birth weight (grams), mean ± SD	1,999.2 ± 669.81	2,248.2 ± 579.34	0.001*
Birth weight			0.001*
Less than 1500 g	33 (19.9)	32 (9.7)	
1,500 – 2,499 g	96 (57.8)	188 (56.8)	
2,500 – 4,000g	37 (22.3)	111 (33.5)	
Apgar score < 7			
At 1 min	42 (25.3)	34 (10.3)	< 0.001*
At 5 min	20 (12.1)	9 (2.7)	< 0.001*
Gender			0.632
Male	96 (57.8)	183 (55.3)	
Female	70 (42.2)	148 (44.7)	
NICU admission	51 (30.7)	31 (9.4)	< 0.001*

BMI: body mass index, SD: standard deviation, n: number of patients, PPROM: preterm premature rupture of membranes, UTI: urinary tract infection, GDM: gestational diabetes, NICU: neonatal intensive care unit
Data are expressed by n (%), mean ± SD.

Table 2. Comparison of maternal laboratory results between the two groups.

Characteristics	Early onset neonatal sepsis, n = 166	Non-early onset neonatal sepsis, n = 331	p value
Hemoglobin (g/dL), mean ± SD	11.5 ± 1.36	11.6 ± 1.20	0.453
Hematocrit (%), mean ± SD	35.2 ± 4.08	35.6 ± 3.53	0.277
White blood cell (cells/μL), mean ± SD	13,749.0 ± 5,086.77	12,365.5 ± 3,718.49	0.001*
Neutrophil (%)	79.5 ± 9.61	77.9 ± 8.59	0.055
Lymphocyte (%)	13.9 ± 7.27	15.2 ± 6.39	0.034*
NLR, median (IQR)	6.6 (3.6, 10.5)	5.2 (3.6, 7.9)	0.022*
Platelet (cells/μL), mean ± SD	261,283.1 ± 72,844.53	251,121.8 ± 62,167.87	0.106

SD: standard variation, g/dL: gram/deciliter, IQR: interquartile range, NLR: neutrophil to lymphocyte ratio, n: number of patients

Data is expressed as mean ± SD, median IQR

In multivariable logistic regression, three maternal factors were independently associated with EONS. Gestational age < 34 weeks was linked to a nearly threefold increased risk (adjusted odds ratio (aOR) 2.77, 95%CI 1.74–4.40, p < 0.001). Chorioamnionitis was also a strong predictor (aOR 3.33, 95%CI 1.21–9.17, p = 0.020), as was maternal leukocytosis (WBC >15,000/μL; aOR 1.92, 95%CI 1.16–3.20, p = 0.012). Other factors, including maternal age, excessive gestational weight gain, PPROM, and NLR > 5, were not significantly associated after adjustment (Table 3).

Table 3. Maternal factors associated with EONS.

Variables	OR (95%CI)	Adjusted OR (95%CI)	p value
Maternal Age (years)			
< 20	0.91 (0.53, 1.57)	0.71 (0.40, 1.26)	0.241
20-34	1	Ref.	
≥ 35	1.45 (0.84, 2.51)	1.39 (0.78, 2.47)	0.263
Excessive weight gain	0.88 (0.54, 1.43)	1.08 (0.65, 1.80)	0.772
PPROM	0.74 (0.51, 1.08)	0.92 (0.71, 1.18)	0.491
Gestational age at delivery < 34 weeks	2.90 (1.98, 4.27)	2.77 (1.74, 4.40)	< 0.001*
Chorioamnionitis	5.38 (2.05, 14.14)	3.33 (1.21, 9.17)	0.020*
Maternal NLR ≥ 5	1.28 (0.88, 1.87)	0.62 (0.38, 1.01)	0.054
Maternal WBC > 15,000 cells/μL	2.11 (1.38, 3.22)	1.92 (1.16, 3.20)	0.012*

PPROM: preterm premature rupture of membranes, OR: odds ratio, CI: confidence interval, NLR: neutrophil-to-lymphocyte ratio, WBC: white blood cell

Discussion

This study found that a maternal factor associated with EONS in preterm neonates was a gestational age of less than 34 weeks, which was significantly associated with EONS (adjusted OR 2.7, 95%CI 1.74–4.40, p < 0.001). This variable was also used for sample size estimation, and the observed association supports the initial hypothesis. This finding was consistent with the study by Chayawongrungreung et al[8], which also reported an association between a gestational age below 34 weeks and EONS in preterm infants. Similarly, the study by Al-Wassia et al[7] found that the lower the gestational age, the higher the risk of developing EONS. This supports the hypothesis that immature immune systems in preterm neonates contribute to an increased susceptibility to infection[15, 16]. Furthermore, preterm neonates born before 34 weeks are more likely to undergo invasive procedures, such as central venous catheterization and endotracheal

intubation, and have prolonged hospital stays, all of which increase the risk of developing EONS[17].

Chorioamnionitis was significantly associated with the occurrence of EONS, with an adjusted OR of 3.33 (95%CI 1.21–9.17, p = 0.02). This finding was consistent with studies by Guo et al[18], Joachim et al[11], and Lee et al[19]. The increased risk of EONS associated with chorioamnionitis is explained by intrauterine inflammation caused by bacterial infection ascending from the lower genital tract into the uterine cavity. The infection can invade the amniotic sac, fetal membranes, and placenta, resulting in inflammation and infection of the fetus before, during, or after delivery. Moreover, the inflammatory process triggers the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, which can induce preterm labor and increase neonatal susceptibility to infection[17, 20, 21].

Maternal WBC > 15,000 cells/μL was also significantly associated with EONS with an adjusted OR of 1.92 (95%CI 1.16-3.20, p = 0.012). This finding was consistent with physiological mechanisms indicating that elevated maternal WBC counts may result from the body's response to infection in the reproductive tract or intrauterine inflammation, which aligns with a diagnosis of chorioamnionitis[20, 21]. In clinical practice, maternal WBC levels are often used as part of the diagnostic criteria and management of suspected intraamniotic infection, a condition also associated with EONS in this study.

This study aimed to identify maternal factors associated with EONS in preterm neonates and was conducted at a tertiary care hospital, which may limit the generalizability of the findings to broader populations. Therefore, the study population may differ from those in primary or secondary care settings. Additionally, demographic characteristics and access to maternal care in this region may not reflect those in other provinces or countries. Nevertheless, the large sample size and comprehensive collection of maternal clinical data enhance the study's internal validity. These findings may still be applicable to similar tertiary hospitals with comparable referral patterns and maternal risk profiles.

The findings offer valuable insights that may support early clinical decision-making, guide clinical management, and increase awareness among obstetricians and pediatricians. This study had several limitations. The retrospective design, reliance on incomplete medical record data, and single center setting, may have led to missing information for certain variables or maternal clinical symptoms. Future prospective studies can overcome these limitations and strengthen the evidence.

Conclusion

This study identified several maternal factors associated with an increased risk of EONS, including chorioamnionitis, gestational age less than 34 weeks, and maternal leukocytosis. This integration offers a promising approach to improving early recognition and perinatal care of mothers and preterm neonates at risk of EONS.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Oral Glucose Powder Solution versus 50% Intravenous Glucose Solution on Blood Glucose Levels and Satisfaction in the 50-gram Glucose Challenge Test: A randomized controlled trial

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ABSTRACT

Objective: To compare blood glucose levels and patient satisfaction during gestational diabetes screening between two oral glucose formulations: 50 grams of dissolved glucose powder in water versus 50% intravenous glucose solution diluted for oral intake.

Materials and methods: This randomized controlled trial was conducted from July 2024 to July 2025. A total of 208 pregnant women were randomly allocated into two equal groups. Group 1 (n = 104) received 50 grams of glucose powder dissolved in water, while Group 2 (n = 104) received 50% glucose solution intended for intravenous injection, also diluted in water. In both groups, the glucose solutions were prepared to a final volume of 300 mL and administered orally. All participants underwent the glucose screening test by drinking the assigned solution. Blood glucose levels were measured one hour after ingestion. The primary outcome was to compare the mean 1-hour post-load plasma glucose between the two groups. The secondary outcome was to compare patient satisfaction regarding the taste and ease of glucose solution consumption between the groups.

Results: There were no significant differences in baseline characteristics between the two groups. Similarly, there was no significant difference in 1-hour post-load plasma glucose. The mean blood glucose level was 119.22 mg/dL in the distilled glucose powder group and 121.25 mg/dL in the 50% intravenous glucose solution group (mean difference = -1.84, 95% confidence interval (CI) -8.62-4.95). There was no statistically significant difference in the proportion of positive glucose challenge test results between the groups (19.23% vs 24.03%, risk ratio 1.25, 95% CI 0.74-2.11, p = 0.703). However, the satisfaction score was significantly higher in the group that drank distilled glucose powder in water compared to the group that drank 50% intravenous glucose solution (p = 0.005).

Conclusion: The administration of 50 grams of glucose powder dissolved in water and 100 milliliters of 50% injectable glucose solution diluted to a total volume of 300 milliliters resulted in no

significant difference in 1-hour post-load plasma glucose levels. However, the consumption of 50 grams of glucose powder was reported to result in ease of ingestion.

Keywords: glucose challenge test, gestational diabetes mellitus, gestational diabetes mellitus, distilled glucose powder, 50% intravenous glucose solution, blood glucose measurement, patient satisfaction

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การรับประทานสารละลายกลูโคสชนิดผงเทียบกับสารละลายกลูโคสเข้าหลอดเลือดดำความเข้มข้น 50% ต่อระดับน้ำตาลในเลือดและความพึงพอใจระหว่างการทดสอบกลูโคสชนิด 50 กรัม: การทดลองแบบสุ่มมีกลุ่มควบคุม

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บทคัดย่อ

วัตถุประสงค์*: เพื่อเปรียบเทียบระดับน้ำตาลในเลือดและความพึงพอใจของผู้ป่วยระหว่างการคัดกรองเบาหวานขณะตั้งครรภ์ ด้วยสารละลายกลูโคสชนิดรับประทานสองรูปแบบ ได้แก่ กลูโคสผง 50 กรัมละลายในน้ำ กับสารละลายกลูโคสร้อยละ 50 ที่ใช้สำหรับฉีดทางหลอดเลือด*

วัสดุและวิธีการ*: การทดลองแบบสุ่มมีกลุ่มควบคุมนี้ดำเนินการระหว่างเดือนกรกฎาคม พ.ศ. 2567 ถึง กรกฎาคม พ.ศ. 2568 โดยหญิงตั้งครรภ์จำนวน 208 คนถูกสุ่มแบ่งออกเป็นสองกลุ่ม กลุ่มที่ 1 (n = 104) ได้รับกลูโคสผง 50 กรัมละลายในน้ำ ส่วนกลุ่มที่ 2 (n = 104) ได้รับกลูโคสชนิดร้อยละ 50 ที่ผลิตสำหรับฉีดทางหลอดเลือด ซึ่งถูกเจือจางในน้ำเช่นกัน ทั้งสองกลุ่มปรับปริมาตรของสารละลายให้เป็น 300 มิลลิลิตร และให้ดื่มทางปาก จากนั้นวัดระดับน้ำตาลในเลือดหลังจากดื่มครบ 1 ชั่วโมง โดยผลลัพธ์หลักของการศึกษา คือ การเปรียบเทียบระดับน้ำตาลในเลือดหลังรับประทานอาหาร 1 ชั่วโมง โดยเฉลี่ยระหว่างกลุ่มทดลองทั้งสองกลุ่ม ส่วนผลลัพธ์รอง คือ ให้ผู้ป่วยเปรียบเทียบความพึงพอใจของผู้ป่วยต่อรสชาติและความสะดวกในการรับประทานสารละลายน้ำตาลระหว่างกลุ่ม*

ผลการศึกษา*: ไม่พบความแตกต่างอย่างมีนัยสำคัญในลักษณะพื้นฐานระหว่างกลุ่มทั้งสอง นอกจากนี้ ยังไม่พบความแตกต่างอย่างมีนัยสำคัญในระดับน้ำตาลในเลือดหลังรับกลูโคส 1 ชั่วโมง โดยระดับเฉลี่ยของกลูโคสในเลือดอยู่ที่ 119.22 mg/dL ในกลุ่มที่ดื่มกลูโคสผง และ 121.25 mg/dL ในกลุ่มที่ดื่มกลูโคส 50% สำหรับฉีด (ค่าความแตกต่างของค่าเฉลี่ย =-1.84, ช่วงความเชื่อมั่นร้อยละ 95 -8.62-4.95).และไม่มีความแตกต่างอย่างมีนัยสำคัญในสัดส่วนของผลการทดสอบน้ำตาลหลังรับประทานน้ำตาล 1 ชั่วโมงที่เป็นบวกระหว่างกลุ่ม (ร้อยละ 19.23 ต่อ 24.03, risk ratio 1.25, 95% CI 0.74-2.11, p =*

0.703) อย่างไรก็ตาม กลุ่มที่ดื่มกลูโคสผงละลายในน้ำมีคะแนนความพึงพอใจในความง่ายของการดื่มสารละลายสูงกว่าอย่างมีนัยสำคัญเมื่อเทียบกับกลุ่มที่ดื่มกลูโคสร้อยละ 50 สำหรับฉีด (p = 0.005)

***สรุปผล**: การดื่มกลูโคสผงละลายในน้ำและการดื่มกลูโคสร้อยละ 50 ที่ใช้สำหรับฉีด ให้ผลระดับน้ำตาลในเลือดหลัง 1 ชั่วโมงที่ไม่แตกต่างกันในการคัดกรองเบาหวานขณะตั้งครรภ์ด้วยการทดสอบน้ำตาลหลังรับประทานน้ำตาล 1 ชั่วโมง อย่างไรก็ตามการรับประทานกลูโคสผงขนาด 50 กรัมดื่มง่ายกว่า*

***คำสำคัญ**: การทดสอบกลูโคส, เบาหวานขณะตั้งครรภ์, กลูโคสผง, กลูโคสร้อยละ 50 สำหรับฉีด, การวัดระดับน้ำตาลในเลือด, ความพึงพอใจของผู้ป่วย*

Introduction

Gestational diabetes mellitus (GDM) is a common and important obstetric complication[1]. It is associated with significant short-term and long-term adverse outcomes for both mothers and their offspring. In the short term, GDM increases the risk of complications such as neonatal hypoglycemia, shoulder dystocia, macrosomia, preeclampsia, postpartum hemorrhage, and even intrauterine fetal demise[1]. In the long term, women with a history of GDM are at significantly higher risk of developing type 2 diabetes mellitus, with a relative risk approximately 7.4 times greater than women without GDM[2]. Furthermore, offspring of mothers with GDM are more likely to develop obesity, glucose intolerance, and metabolic syndrome later in life[1].

The prevalence of GDM has been reported to vary across countries. According to the International Diabetes Federation (IDF), approximately 21.1 million women, or 16.7% of pregnancies globally, are affected by hyperglycemia during pregnancy[3]. The prevalence of diabetes in pregnancy differs significantly between regions. For instance, in the United States, GDM occurs in approximately 7.8% of live births[4]. In Thailand, the 2019 IDF report indicated that the country had the highest prevalence of GDM in Southeast Asia, at 24.7%. However, the reported prevalence of GDM in Thailand has varied across studies, ranging from 12.3-21.8%[5-7], largely due to differences in screening criteria and testing methods used during pregnancy.

The glucose challenge test (GCT) and oral glucose tolerance test (OGTT) are standard methods for screening and diagnosing GDM[8]. For these tests, 50 to 100 grams of glucose powder dissolved in 300 milliliters of water is commonly recommended[9]. The new International Federation of Obstetrics and Gynaecology guidelines on GDM recommend the use of anhydrous glucose powder dissolved in a glass of water as part of the one-step screening approach[10]. However, due to the wide availability of 50% glucose solution intended for intravenous injection, many hospitals in Thailand have adopted this preparation as an alternative to glucose powder for both GCT and OGTT. While glucose powder is generally easier to dissolve, the injectable glucose solution is readily available and more convenient for use in most clinical settings. Although the use of intravenous glucose solution for the 50-gram glucose challenge test in GDM screening has been practiced for many years, no studies have confirmed whether the mean plasma glucose levels differ compared with glucose powder. Schwartz, et al[11] previously reported that, despite an equivalent total glucose load, differences in the form of glucose preparation may influence plasma glucose levels. This rationale formed the basis of the present

study.

Despite these practical differences, a review of the existing literature found no published studies comparing the two glucose formulations in terms of their effects on blood glucose levels, the proportion of positive screening results, or patient satisfaction. Therefore, this study was conducted to generate evidence-based recommendations that may help inform and improve GDM screening practices in hospital settings.

Materials and Methods

The present study was a randomized controlled trial conducted at the Department of Obstetrics and Gynecology, Udon Thani Hospital, Udon Thani, Thailand, between July 2024 and July 2025. The study protocol was approved by the Udon Thani Hospital Ethics Committee in Human Research (No. 121/2567) and was registered in the Thai Clinical Trials Registry (TCTR), with the identification number TCTR20241201003.

A total of 208 pregnant women, between 24 and 28 weeks of gestation, who underwent universal GDM screening as recommended by the Royal Thai College of Obstetricians and Gynaecologists, were enrolled[11]. The inclusion criteria were age ≥ 18 years and a singleton pregnancy. Exclusion criteria included pre-existing diabetes mellitus or unwillingness to participate in the study. All participants were informed of the study details prior to undergoing the GCT at the antenatal care clinic, and written informed consent was obtained from each participant.

Randomization was performed using computer-generated numbers. Allocation was concealed in sealed, opaque envelopes prepared by research assistants. Eligible participants were randomly assigned into one of two groups: the first group received 50 grams of glucose powder (n = 104), and the second group received 100 milliliters of 50% intravenous glucose solution (n = 104), both diluted with water to give a total volume of 300 milliliters before oral ingestion.

Pregnant women were randomly assigned to one of two groups, and the patients were blinded to their group allocation, and the medical technologists were also blinded to the group assignments. Group 1 received 50 grams of glucose powder dissolved in water to a final volume of 300 milliliters. Group 2 received 100 milliliters of 50% injectable glucose solution (equivalent to 50 grams of glucose), diluted with water to a total volume of 300 milliliters11. However, the taste of the two glucose formulations differed, with the 50% intravenous glucose solution perceived as sweeter than the glucose powder solution.

Participants in both groups were not required to fast prior to the test. One hour after ingestion of the glucose solution, venous blood samples were collected to measure plasma glucose levels using the hexokinase enzymatic method with the Architect c4000 analyzer (Abbott Laboratories, USA). The secondary outcome was to compare patient satisfaction regarding the taste and ease of glucose solution consumption between the groups, as assessed by the study participants.

The sample size was calculated using the formula for comparing the means of the two independent groups, based on the primary objective of the study. The calculation was performed using the n4Studies application[13,14]. The estimated mean blood glucose level in the control group was 127.40 mg/dL, compared to 114.66 mg/dL (representing a 10% difference) in the treatment group, with a standard deviation of 31.7 mg/dL in both groups15. Allowing for an anticipated dropout rate of 10%, the final required sample size was determined to be 104 participants per group.

Statistical analysis was performed using STATA software version 13 (StataCorp, College Station, TX, USA). Continuous variables were reported as means and standard deviations, while categorical variables were presented as frequencies and percentages. An unpaired t-test was used to compare continuous variables between groups, and results were presented with mean differences and 95% confidence intervals (CIs). A generalized linear model was applied to

estimate relative risks (RRs) and their corresponding 95% CIs. The Pearson chi-square test and Fisher's exact test were used to compare categorical variables. A p value of < 0.05 was considered statistically significant.

Results

A total of 212 pregnant women were enrolled in the study, and 4 were excluded (1 was unwilling to participate and 3 were pre-existing diabetes mellitus). All participants were randomly assigned into two equal groups. Blood samples were collected exactly one hour after ingestion to measure blood glucose. The study flow is shown in Fig. 1.

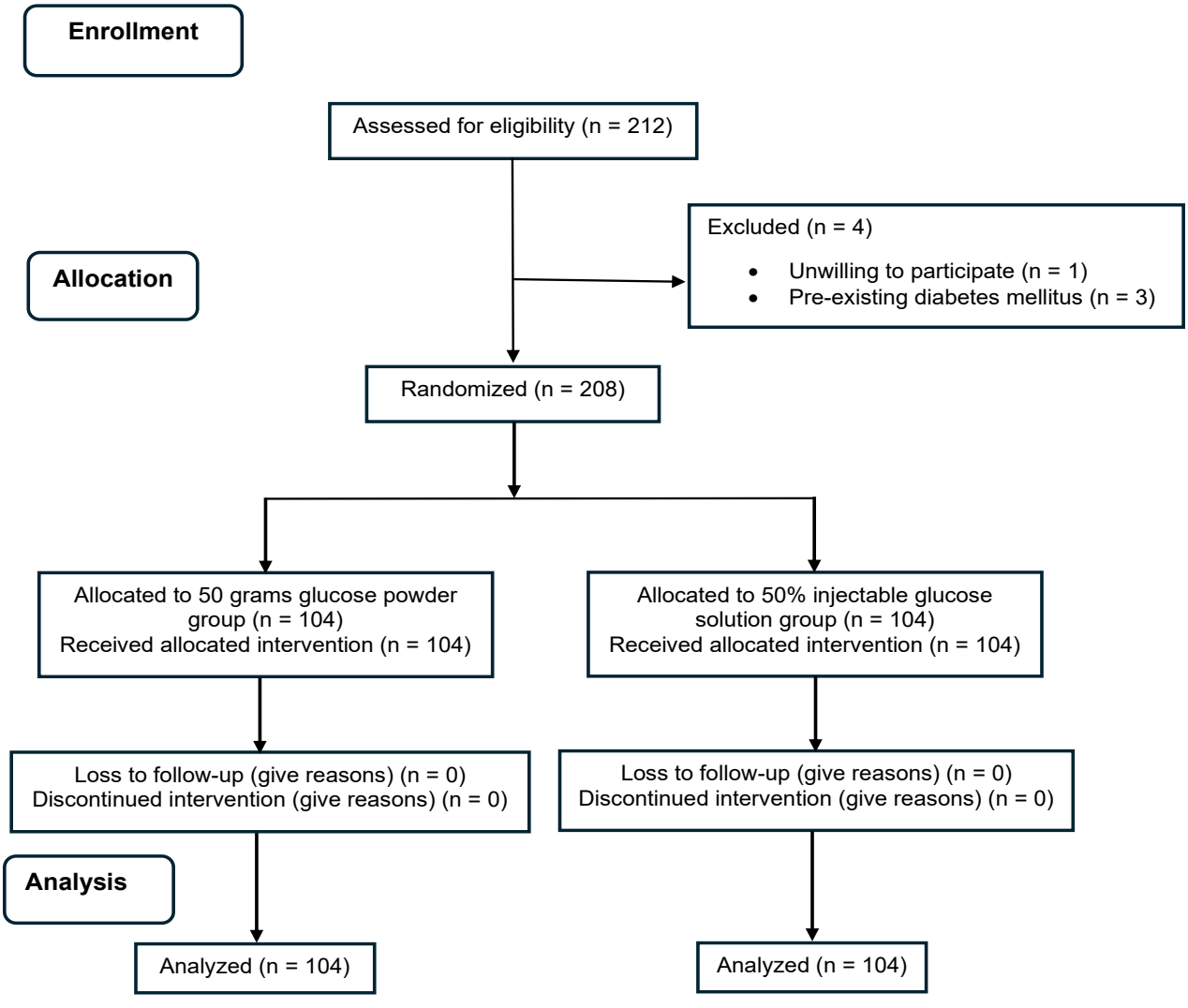

Fig. 1.

There were no significant differences between the two groups in baseline demographic and clinical characteristics, including maternal age, body mass index (BMI), parity, and gestational age at the time of testing, as presented in Table 1.

Table 1. Clinical characteristics of oral glucose and group.

	50-gram glucose powder group (n = 104)	50% glucose solution group (n = 104)	p value
Age, mean ± SD (weeks)	25.86 ± 5.62	26.96 ± 5.45	0.151*
Body mass index, mean ± SD (weeks)	22.85 ± 4.78	23.69 ± 4.47	0.195*
Nulliparity, n (%)	46 (44.23%)	40 (38.46%)	0.398**
Gestational age at testing, mean ± SD (weeks)	25.56 ± 1.25	25.59 ± 1.27	0.869*

* Calculated by unpaired t-test, ** calculated by pearson chi square

SD: standard deviation

The GCT results demonstrated that the mean 1-hour post-load plasma glucose were 119.33 mg/dL in the group receiving 50 grams of glucose powder and 121.05 mg/dL in the group receiving 100 milliliters of 50% injectable glucose solution. The mean difference with 95%CI was -1.84 (-8.62 to 4.95) mg/dL, indicating no statistically significant difference between the two groups. The positive GCT rate also showed no significant difference between the two groups. However, the ease of ingestion scores was higher in the 50-gram powder group (Table 2). Nevertheless, no significant differences were observed between the groups in taste satisfaction or in adverse events such as nausea and vomiting.

Table 2. Comparison of primary and secondary outcomes between groups.

	50-gram glucose powder group (n = 104)	50% glucose solution group (n = 104)	Risk ratio (95%CI) or mean difference (95% CI)
Positive GDM screening, n (%)	20 (19.23%)	25(24.03%)	1.25 (0.74 to 2.11) p = 0.703**
Plasma glucose (mg/dL), mean ± SD	119.22 ± 24.13	121.05 ± 25.49	-1.84 (-8.62 to 4.95) p = 0.703**
Satisfaction score (mean ± SD)			
Taste	3.98 ± 0.75	3.82 ± 0.89	0.16 (-0.06 to 0.39) p = 0.076*
Ease of ingestion	4.20 ± 0.84	3.88 ± 0.91	0.32 (0.08 to 0.56) p = 0.005*
Solubilit	4.05 ± 0.81	3.91 ± 0.78	0.14 (-0.08 to 0.35) p = 0.110*
Side effect			
Nausea	3 (2.88%)	4 (3.85%)	1.33 (0.31-5.81) p = 0.500 ***

*Calculated by unpaired t-test, ** calculated by Pearson chi-square, *** calculated by Fisher's extract test

SD: standard deviation

Discussion

This study demonstrated that the 1-hour blood glucose levels following ingestion of 50 grams of glucose powder and 100 milliliters of 50% injectable glucose solution were not significantly different. The incidence of adverse effects, such as nausea and vomiting, was also comparable between the two groups during the 50-gram glucose challenge test for GDM screening. However, ingestion of glucose powder was found to be easier and resulted in higher participant satisfaction.

The present study was conducted to address a practical concern in antenatal care regarding the form of glucose administration during the 50-gram GCT, which is widely used for GDM screening. Although the World Health Organization and other clinical guidelines provide recommendations on the glucose load, they do not specify the exact formulation, thereby allowing healthcare providers to choose between glucose powder and injectable glucose solutions diluted for oral administration16. In many clinical settings, particularly in primary and secondary hospitals, glucose powder is not always readily available, and injectable glucose solution is often used as an alternative. Despite this common practice, there has been a lack of direct evidence comparing the efficacy, tolerability, and acceptability of these two formulations in a standardized screening context. To our knowledge, this is the first randomized controlled trial that directly compares 1-hour plasma glucose levels, adverse effects, and maternal satisfaction between these two forms of glucose delivery.

Our findings demonstrated that both formulations produced comparable glycemic responses, with no statistically significant differences in 1-hour blood glucose levels. Moreover, the incidence of adverse effects such as nausea and vomiting was similar between groups, indicating that both methods are equally safe and well-tolerated. Importantly, however, participants who received glucose powder reported greater ease of ingestion and higher satisfaction compared to those who consumed diluted injectable glucose solutions. These results suggested that while both formulations are effective for GCT, glucose powder may be favored due to higher patient acceptability and ease of use.

Previous studies have reported that glucose solution can cause gastrointestinal side effects due to delayed gastric emptying and its intensely sweet taste, particularly when consumed in large volumes[17]. Schwartz et al found that using a more physiologic, lower-osmolarity glucose solution reduced nausea and vomiting without affecting glucose values at 1 hour[11]. Other studies also highlighted that patient satisfaction and perceived tolerability vary depending on glucose formulation, flavoring, and even texture18-19. These findings support the significance of our results and emphasize the importance of patient-centered approaches when selecting GCT methods.

This study had several strengths. It was conducted using a randomized controlled design, which minimizes selection bias and strengthens internal validity. The sample size was adequate to detect meaningful differences in glycemic response and adverse effects, and the study protocol closely reflected real-world clinical practice. Furthermore, patient-reported outcomes, such as satisfaction and ease of ingestion, were included, with patients blinded to which solution they received, providing a more comprehensive and unbiased perspective.

Nevertheless, some limitations should be acknowledged. This study was conducted at a single center, which may limit the generalizability of the findings to other populations or settings. Although both groups received the same total volume of glucose solution, subjective responses may have been influenced by differences in taste and mouthfeel. Furthermore, the study did not evaluate clinical outcomes or the diagnostic accuracy of the GCT results. The sample size calculation was based solely on the primary objective and did not account for patient satisfaction. Additionally, certain variables, such as the time since the last meal and specific risk

factors for GDM, were not included in the analysis of this study.

Given the practical implications of our findings, oral glucose powder is generally more satisfaction in terms of ease of ingestion, however the supply availability in some centers still might be problematic.

Future studies could expand on this work by examining commercial glucose beverages or flavored options, and by testing acceptability in women with conditions such as hyperemesis gravidarum. Multicenter studies in varied clinical contexts would help strengthen generalizability. Cost-effectiveness analysis may also help inform policy decisions regarding which formulations to use in standard GDM screening protocols.

In conclusion, this study supported the interchangeability of glucose powder and diluted injectable glucose for GDM screening in terms of glycemic outcomes and safety. However, glucose powder may be the preferred option due to higher maternal satisfaction, and healthcare providers should consider patient experience in selecting formulations for GCT administration.

Conclusion

The administration of 50 grams of glucose powder dissolved in water and 100 milliliters of 50% injectable glucose solution diluted to a total volume of 300 milliliters resulted in no significant difference in 1-hour post-load plasma glucose blood glucose levels. However, the consumption of 50 grams of glucose powder was preferable due to the higher score of ease of ingestion.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Survival Analysis and Proportion of Lymph Node Metastasis of Early-stage HPV-associated Endocervical Adenocarcinoma Based on Pattern

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ABSTRACT

Objectives: To determine disease-free survival, disease-specific survival and lymph node metastasis in human papilloma virus (HPV) - associated cervical adenocarcinoma by pattern-based classification.

Materials and Methods: A total of 98 cases diagnosed with HPV-associated cervical adenocarcinoma that underwent pelvic lymph node dissection were retrospectively reviewed and reclassified according to the latest World Health Organization classification.

Results: Ninety-three were classified as usual-type adenocarcinoma (94.9%) and 5 (5.1%) as mucinous adenocarcinoma. 19 (19.4%), 32 (32.7%), and 47 (47.6%) cases as patterns A, B, and C, respectively. Lymph node metastasis was observed in 0% of pattern A tumors, 12.5% of pattern B tumors, and 31.9% of pattern C tumors. The 5-year disease-specific survival of patients with patterns A, B, and C tumors was 100%, 90.6%, and 63.8 %, respectively. The 5-year disease-free survival of patients with patterns A, B, and C tumors was 94.7%, 84.4%, and 57.4%, respectively. Patten C tumors were associated with worst disease-specific survival and disease-free survival: hazard ratio 8.82 (95% confidence interval (CI) 1.70 to 66.41) and 10.74 (95% CI 1.4 to 78.13), but the association disappeared after adjustment for clinicopathologic characteristics.

Conclusion: The 5-year disease-specific survival was 100% with no lymph node metastasis in patients with pattern A. Patients with pattern B and C are associated with higher risk of lymphovascular space invasion and lymph node metastasis.

Keywords: pattern-based classification, HPV-associated cervical adenocarcinoma, usual-type endocervical adenocarcinoma, disease-free survival, disease-specific survival.

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การวิเคราะห์การรอดชีพ และอัตราส่วนของการแพร่กระจายไปยังต่อมน้ำเหลือง ของโรคมะเร็งปากมดลูกที่สัมพันธ์กับเชื้อ HPV ระยะเริ่มต้น อ้างอิงจากรูปแบบ

ชัย อริยศรีวัฒนา, ณัฏฐ์กฤตา โพธิพรธวัฒน์, พฐ ตัณฑ์ไพโรจน์, สุรางค์ ตรีรัตนชาติ

บทคัดย่อ

วัตถุประสงค์: *เพื่อค้นหาระยะเวลาปลอดจากโรค ระยะเวลารอดชีวิตจำเพาะโรค และการแพร่กระจายไปยังต่อมน้ำเหลืองของโรคมะเร็งปากมดลูกที่สัมพันธ์กับเชื้อ HPV ระยะเริ่มต้น อ้างอิงจากการแบ่งประเภทตามรูปแบบ*

วัสดุและวิธีการ: *ได้ทำการทบทวนย้อนหลังและจัดการแบ่งประเภทของผู้ป่วยโรคมะเร็งปากมดลูกที่สัมพันธ์กับเชื้อ HPV ระยะเริ่มต้นที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองในอุ้งเชิงกรานทั้งหมด 98 คน โดยอ้างอิงการแบ่งประเภทตามองค์การอนามัยโลก*

ผลการศึกษา: *ผู้ป่วย 93 คนได้ถูกจัดเป็นมะเร็งชนิดต่อมแบบทั่วไป (ร้อยละ 94.9) และ 5 คนได้ถูกจัดเป็นมะเร็งชนิดต่อมแบบเยื่อเมือก (ร้อยละ 5.1) โดยการแบ่งประเภทตามรูปแบบ พบเป็นรูปแบบ A 19 คน (ร้อยละ 19.4) รูปแบบ B 32 คน (ร้อยละ 32.7) รูปแบบ C 47 คน (ร้อยละ 47.6) พบการกระจายโรคไปยังต่อมน้ำเหลืองในอุ้งเชิงกราน ร้อยละ 0 ในรูปแบบ A ร้อยละ 12.5 ในรูปแบบ B ร้อยละ 31.9 ในรูปแบบ C ระยะเวลารอดชีวิตจำเพาะโรค 5 ปี ในรูปแบบ A อยู่ที่ร้อยละ 100 รูปแบบB อยู่ที่ร้อยละ 90.6 และรูปแบบ C อยู่ที่ร้อยละ 63.8 ระยะเวลาปลอดจากโรค 5 ปี ในรูปแบบ A อยู่ที่ร้อยละ 94.7 รูปแบบB อยู่ที่ร้อยละ 84.4 และรูปแบบ C อยู่ที่ร้อยละ 57.4 รอยโรครูปแบบ C สัมพันธ์กับระยะเวลารอดชีวิตจำเพาะโรคและระยะเวลาปลอดจากโรคที่แย่ที่สุด (hazard ratio 8.82 (95% confidence interval (CI) 1.70 to 66.41) และ 10.74 (95% CI 1.4 to 78.13) แต่ความสัมพันธ์นี้หายไปเมื่อมีการปรับเปรียบเทียบกับคุณลักษณะทางคลินิกและพยาธิวิทยา*

สรุป: *ระยะเวลารอดชีวิตจำเพาะโรค 5 ปี ในรูปแบบ A อยู่ที่ร้อยละ 100 โดยไม่พบการกระจายโรคสู่ต่อมน้ำเหลืองในอุ้งเชิงกราน ผู้ป่วยในรูปแบบ B และ C สัมพันธ์กับความเสี่ยงที่มากขึ้นต่อการบุกรุกสู่ระบบน้ำเหลืองและหลอดเลือดและกระจายโรคสู่ต่อมน้ำเหลือง*

คำสำคัญ: *การแบ่งประเภทตามรูปแบบ, โรคมะเร็งปากมดลูกที่สัมพันธ์กับเชื้อ HPV, มะเร็งปากมดลูกชนิดต่อมแบบทั่วไป, ระยะเวลาปลอดจากโรค, ระยะเวลารอดชีวิตจำเพาะโรค*

Introduction

Cervical cancer is the fourth most common cancer in women globally and is a leading cause of cancer-related death in women of sub-Saharan Africa[1]. Both the International Federation of Gynecology and Obstetrics (FIGO) and tumor node metastasis (TNM) staging systems of cervical cancer require microscopic depth of invasion in both squamous cell and adenocarcinoma morphology[2]. The treatment of cervical cancer is either surgical treatment or radiation. If the choice is surgical treatment, the identification of candidates for surgery with lymphadenectomy is imperative because lymph node dissection is associated with a risk of complications, including lymphocele formation, thromboembolic events, vascular injury, nerve injury, and ureteral injury[3]. According to the recent National Comprehensive Cancer Network (NCCN) guidelines[4], individuals with microinvasive cervical cancer (stage IA1) without lymphovascular space invasion (LVSI) have less than a 1% chance of lymph node metastasis; thus, lymphadenectomy is not recommended. However, in cervical adenocarcinoma, compared with squamous cell carcinoma, the depth and horizontal spread of invasion are sometimes problematic and difficult to determine[5], which leads to unnecessary lymphadenectomy and an increased risk of complications. There is a need for predictive factors for cervical adenocarcinoma in order to reduce the unnecessary complication from lymphadenectomy.

To objectively identify better predictive factors in cervical adenocarcinoma, a pattern-based system was developed for this cancer[6-7]. This pattern-based system classifies cervical adenocarcinoma into three patterns (patterns A, B, and C). This system is based on patterns of stromal invasion, LVSI, and confluent growth. Depth of invasion and horizontal spread are not considered. In this system, patients with pattern A cervical adenocarcinoma do not develop lymph node metastasis, while 23.3% of patients with pattern C cervical adenocarcinoma develop it. Patients with pattern B tumors only develop lymph node metastasis if LVSI is present. Interobserver variability of this pattern-based classification shows fair to almost perfect agreement[8-10].

Studies show that pattern-based classification is better than FIGO staging to identify tumors with low to no risk of lymph node metastases[11-18]. This is now included in essential criteria of human papilloma virus (HPV) -associated adenocarcinoma of the uterine cervix in the World Health Organization (WHO) classification of tumors[19]; moreover, The International Society of Gynecological Pathologists recommends the use of pattern-based classification for HPV-associated endocervical adenocarcinoma[20]. Using pattern-based classification of HPV-independent cervical adenocarcinoma is not recommended because most are pattern C tumors and are associated with a poor prognosis[16,18, 20-21]. In this study, we aimed to apply the pattern-based classification to our HPV-associated cervical adenocarcinoma cases to determine the proportion of lymph node metastasis, to determine disease-specific and disease-free survival and to identify independent prognostic factors.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) of Institutional Review Board, Faculty of Medicine, Chulalongkorn (IRB No. 248/64). Cases were retrieved from the hospital database. All clinical and pathological data were anonymized. The hospital director and the IRB were informed of our study. We collected data on consecutive cases from January 2011 to December 2015. Infinite population proportions were used for sample size calculation with the main objective being the proportion of lymph node metastasis in pattern C tumor[12].

The selection criteria were as follows: (1) HPV-associated cervical adenocarcinoma (according to WHO criteria) and (2) open surgical removal of the tumor with standard pelvic lymphadenectomy, defined as dissection to separate fibrofatty tissue containing lymph nodes from surrounding pelvic structures, bound distally by the circumflex iliac vein and Cloquet's node, laterally by the genitofemoral nerve, medially by the bladder and internal iliac

vessels, and proximally by the bifurcation of the common iliac artery. In every case, all the cervical tissue was entirely submitted for microscopic examination, per our institution protocol. Immunohistochemical studies were not included in cases with usual-type morphology, because there is a high correlation between HPV-associated pathogenesis and morphology[21]. However, in cases with significant mucinous differentiation, confirmation with p16 immunohistochemistry was performed. Staging of the tumor was assigned according to the FIGO 2009 classification.

We reviewed all adenocarcinoma cases and then reclassified each case according to the recent WHO criteria[19]. Initially, 106 cases were retrieved from our archive: 2 were excluded due to poor quality of slides and paraffin blocks, and 11 cases were classified as adenocarcinoma with significant mucinous morphology. p16 immunohistochemistry testing was applied to all 11 cases with significant mucinous differentiation. Positivity was defined as strong-block type staining. Of those 11 cases, 5 cases showed strong-block type staining and were classified as mucinous adenocarcinoma. The remaining 6 cases showed non-reactive or incomplete staining and were classified as HPV-independent adenocarcinoma (gastric-type adenocarcinoma). All cases and slides were independently reviewed by four pathologists (C.A., N.P., P.T., S.T.). When discrepancies arose, each case was reviewed as a group until a consensus was reached.

We used criteria from the original studies mentioned in the WHO classification of tumors (Fig. 1)[6-7, 18]. Pattern A tumor shows well-demarcated glands with rounded contours; lack of solid growth (i.e., architecturally well to moderately differentiated); no LVSI. Pattern B tumor shows individual or small groups of tumor cells, separated from the round glands, focally desmoplastic or inflamed stroma. Pattern C tumor shows diffuse infiltrative glands with associated extensive desmoplastic response, angulated glands architecture, with interspersed open glands. Data analyzed included patient age at diagnosis, menopausal status, tumor type, FIGO stage, histologic grade, tumor depth and width, LVSI status, lymph node status, postoperative chemotherapy and radiotherapy, disease-specific survival, and disease-free survival.

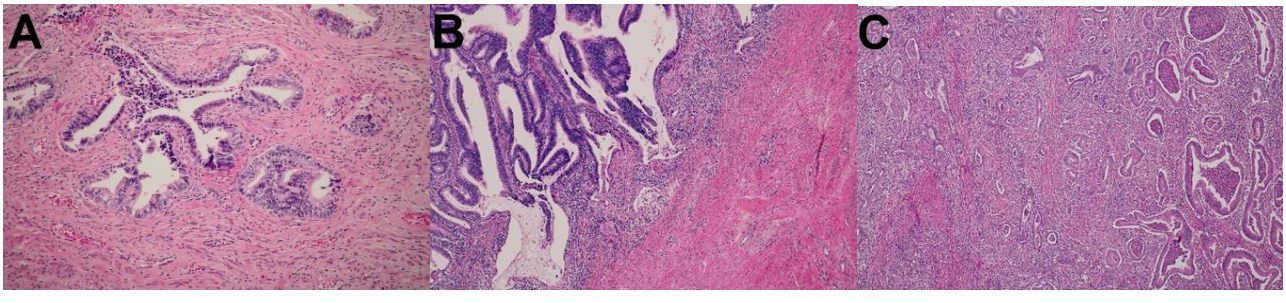

Fig. 1. A: Pattern A tumor shows well-demarcated glands with rounded contours; lack of solid growth (i.e., architecturally well to moderately differentiated); no LVSI. B: Pattern B tumor shows individual or small groups of tumor cells, separated from the round glands; focally desmoplastic or inflamed stroma. C: Pattern C tumor shows diffuse infiltrative glands with associated extensive desmoplastic response; Angulated glands architecture, with interspersed open glands.

Statistical analyses were performed using SPSS software version 22. Chi square test and Fisher's exact test were used to analyze categorical variables. Numerical variables were analyzed by descriptive statistics and were compared using the Kruskal–Wallis's test and One-way analysis of variance (ANOVA). Disease-specific survival (DSS) refers to time from treatment until death from HPV-

associated endocervical adenocarcinoma. Disease-free survival (DFS) refers to time from treatment until the recurrence of disease or death. Disease-specific survival and disease-free survival were analyzed using the Kaplan–Meier method. Comparisons of the survival curve were analyzed by the log-rank test. Cox proportional hazards models were used to test the association of pattern and DSS and DFS in univariable models and in multivariable models, adjusted for clinicopathologic characteristics, using a backward stepwise selection approach to identify independent prognostic factors. A $p < 0.05$ was considered statistically significant.

Results

123 cases of endocervical adenocarcinoma were selected from the database, 17 cases without lymph node specimens, 2 cases with poor quality slides and paraffin blocks and 6 cases with HPV-independent adenocarcinoma were excluded. A total of 98 patients were included (Fig. 2). The patient characteristics are described in Table 1. When the pattern groups were compared, no statistically significant difference was observed in age, menopausal status, lymph node yield or histologic type. The mean lymph node yield was 11 lymph nodes per case (the 25^{th} - 75^{th} percentile range was 8 to 13). Most of our cases had stage I disease, including 100% (19 cases) of pattern A, 90.6% (29 cases) of pattern B, and 89.36% (42 cases) of pattern C. The mean tumor depth of pattern A, B, and C tumors were 4.6, 6.4, and 8.1 mm, respectively. The mean tumor width of pattern A, B, and C tumors were 5, 7.7, and 10 mm, respectively. Statistically significant differences were found in tumor depth and width between the groups ($p = < 0.001$ and $p = 0.001$).

No lymph node metastasis was observed in 19 patients with pattern A tumors, whereas 4 (12.5%) and 15 (31.9%) of patients with pattern B and C tumors had lymph node metastasis. 4 (12.5%) and 17 (36.2%) of patients with pattern B and C tumors, respectively, had LVSI.

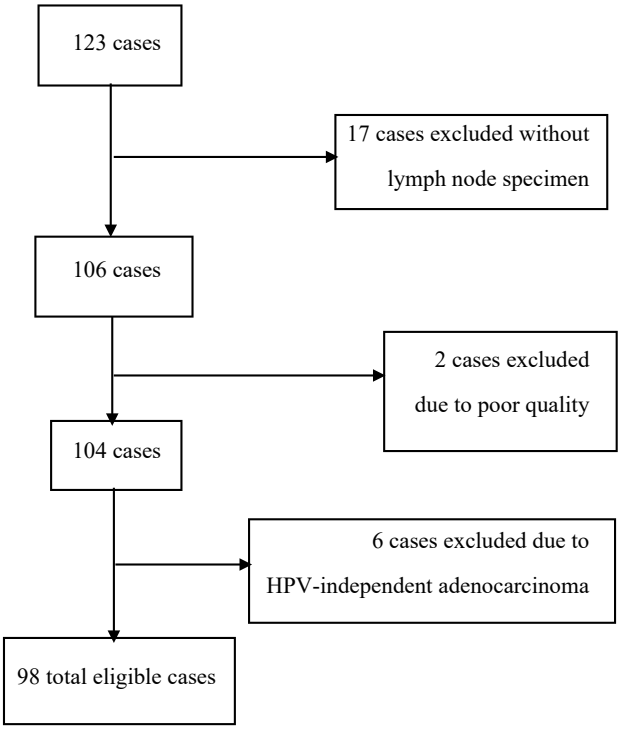

Fig. 2. Study flow.

HPV: human papilloma virus

Table 1. Clinicopathological parameters of patients with pattern-based classification.

Parameter	Pattern A n = 19 (19.4%)	Pattern B n = 32 (32.7%)	Pattern C n = 47 (iu47.6%)	p value
Age (years) (mean (SD))	45 (11.9)	48.5 (7.7)	48.2 (13.5)	0.615
Histological type	Usual 17 Mucinous NOS 2	Usual 32	Usual 44 Mucinous NOS 3	0.219
Stage IA	10	11	8	0.094
IB	9	18	34	
IIA	0	3	5	
Lymph node yield (mean)	9.60	10.55	11.44	0.068
LN metastasis (%)				
Yes	0 (0)	4 (12.5)	15 (31.9)	0.004
No	19 (100)	28 (87.5)	32 (68.1)	
LVSI (%)				
Yes	0 (0)	4 (12.5)	17 (36.2)	< 0.001
No	19 (100)	28 (87.5)	30 (63.8)	
Recurrence (%)				
Yes	1 (5.3)	6 (18.7)	27 (57.4)	0.004
No	18 (94.7)	26 (81.2)	20 (42.5)	
Death (%)				
Yes	1 (5.3)	3 (9.4)	17 (36.2)	0.003
No	18 (94.7)	29 (90.6)	30 (63.8)	
Mean tumor depth (mm) (mean (SD))	4.6 (1.6)	6.4 (3.8)	8.1 (3.8)	0.001
Mean tumor width (mm) (mean (SD))	5 (4.2)	7.7 (4.5)	10.3 (5.5)	< 0.001
Chemotherapy (%)				
Yes	4 (21.1)	21 (65.6)	19 (40.4)	0.007
No	15 (78.9)	11 (34.4)	28 (59.6)	
Radiotherapy (%)				
Yes	5 (31.6)	15 (46.9)	32 (68.1)	0.006
No	14 (68.4)	17 (53.1)	15 (31.9)	
Tumor grading (%)				
Well	17 (89.5)	25 (78.1)	16 (34)	< 0.001
Moderated	1 (5.2)	6 (18.8)	22 (46.8)	
Poorly	1 (5.2)	1 (3.1)	9 (19.1)	
Menopause (%)				
Yes	7 (36.8)	13 (41.9)	16 (34)	0.779
No	12 (63.2)	18 (58.1)	31 (66)	

SD: standard deviation, NOS: not otherwise specified, LN: lymph node, LVSI: lymphovascular space invasion, mm: millimeter

Analysis of recurrent disease and survival

The 5-year disease-specific survival was 100%, 90.6%, and 63.8% in patients with pattern A, B, and C tumors, respectively. The 5-year disease-free survival was 94.7%, 84.4%, and 57.45% in patients with pattern A, B, and C tumors, respectively. One

patient with pattern A (5.3%), 6 patients with pattern B (18.7%) and 27 patients with pattern C (57.4%) tumor recurred. During the follow up period, 18 patients with pattern A (94.7%), 26 patients with pattern B (90.6%) and 30 patients with pattern C (63.8%) survived (Fig. 3).

Univariate Cox regression analysis and multivariate Cox proportional hazards regression analysis were performed to assess the impact of age, mucinous subtype, FIGO stage II, lymph node metastasis, tumor depth and width, tumor grading, menopause status, and lymph node yield on DFF and DSS (Table 2). In univariate analysis, pattern C tumor, FIGO stage II, presence of lymph node metastasis, and menopause status were significantly associated with an increased risk of disease-specific death and recurrence. In multivariate analysis, FIGO stage II hazard ratio (HR) 8.88, 95%CI 2.92– 27.03) and presence of lymph node metastasis (HR 10.43, 95%CI 3.59-30.31) were significantly associated with an increased risk of disease-specific death and recurrence and FIGO stage II (HR 3.72, 95%CI 1.47-9.46) and presence of lymph node metastasis (HR 4.29, 95%CI 1.82-10.13) were significantly associated with an increased risk of recurrence.

The patient with pattern A that died of the disease in our study was a 36-year-old woman who presented with postcoital bleeding. Physical examination revealed a cervical mass with a gross measurement of 3.2 x 2.5 x 1.3 cm, and pelvic examination initially suspected a parametrial invasion. However, after further investigation with computerized tomography (CT) scan, the parametrium was considered to be free of tumor invasion (stage IB1) and radical hysterectomy with bilateral lymph node lymphadenectomy was offered. Forty-seven months after surgery, she developed a lung mass, and a biopsy confirmed recurrent cervical adenocarcinoma. She received chemotherapy (paclitaxel with bevacizumab for 9 treatment cycles and carboplatin with bevacizumab for another 9 treatment cycles), but after a follow-up with CT scan, the lung mass had increased in size. Second-line chemotherapy (topotecan with bevacizumab) was administered, but the disease progressed and she succumbed to the disease at 84 months after surgery.

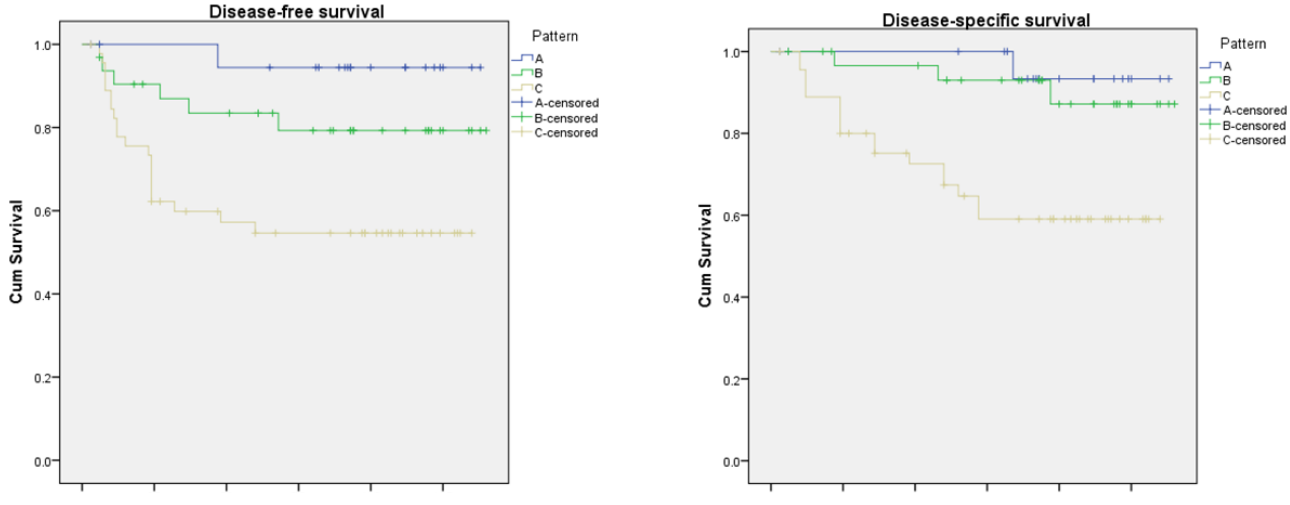

Fig. 3. Disease-free survival and disease-specific survival. The 5-year disease-free survival was 94.7%, 84.4%, and 57.45% and the 5-year disease-specific survival was 100%, 90.6%, and 63.8% in patients with pattern A, B, and C tumors, respectively. The Log-rank p value = 0.002 and 0.004 for disease-specific survival and disease-free survival, respectively.

Table 2. Univariable and multivariable analysis of prognostic factors of overall survival and disease-free survival.

Variable	Disease-specific survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	aHR (95%CI)	p value	HR (95%CI)	p value	aHR (95%CI)	p value
Pattern A	Reference		Reference		Reference		Reference	
Pattern B	1.95 (0.20-18.74)	0.563	1.39 (0.13-14.53)	0.783	4.02 (0.48-33.37)	0.198	3.13 (0.37-26.46)	0.294
Pattern C	8.82 (1.70-66.41)	0.035	4.34 (0.47-40.11)	0.195	10.74 (1.4-78.13)	0.022	4.06 (0.50-33.01)	0.190
Age < 45	Reference				Reference			
Age > 45	2.03 (0.82-5.03)	0.126			1.69 (0.77-3.69)	0.188		
Usual type	Reference				Reference			
Mucinous type	0.70 (0.09-5.24)	0.731			0.50 (0.07-3.70)	0.499		
Figo stage I	Reference		Reference		Reference		Reference	
Figo stage II	11.02 (4.41-27.52)	< 0.001	8.88 (2.92-27.03)	< 0.001	8.26 (3.56-18.92)	< 0.001	3.72 (1.47-9.46)	0.006
LN metastasis								
No	Reference		Reference		Reference		Reference	
Yes	12.84 (5.08-32.47)	< 0.001	10.43 (3.59-30.31)	< 0.001	7.50 (3.44-16.36)	< 0.001	4.29 (1.82-10.13)	0.001
LVSI								
No	Reference				Reference			
Yes	2.63 (1.09-6.38)	0.032			2.42 (1.11-5.29)	0.027		
Tumor depth ≤ 5 mm	Reference				Reference			
Tumor depth > 5 mm	2.18 (0.94-5.09)	0.070			2.45 (1.17-5.16)	0.018		
Tumor width ≤ 7 mm	Reference				Reference			
Tumor width > 7 mm	0.68 (0.29-1.59)	0.377			0.80 (0.38-1.69)	0.565		
Well differentiated	Reference				Reference			
Moderately and poorly differentiated	1.29 (0.61-2.73)	0.511			1.57 (0.59-2.60)	0.078		
Menopause								
No	Reference				Reference			
Yes	3.24 (1.32-7.92)	0.010			2.99 (1.36-6.47)	0.006		
Lymph node yield								
≤ 11	Reference				Reference			
> 11	0.76 (0.31-1.87)	0.546			1.10 (0.51-2.38)	0.800		

CI: confidence interval, HR: adjusted hazard ratio, FIGO: International Federation of Gynecology and Obstetrics, LVSI: lymphovascular space invasion

Discussion

With recent advances in our knowledge of cervical adenocarcinoma, we recognize that an accurate assessment of the depth of invasion in cervical adenocarcinoma can be difficult and lead to unnecessary invasive surgery and lymphadenectomy[4-5]. Another recent recommendation is to classify cervical adenocarcinoma into HPV-associated and HPV-independent tumors[19-21]. Incorporation of a pattern-based classification in the diagnosis of HPV-associated cervical adenocarcinoma is encouraged and may be useful for guiding treatment and for determining prognostic factors. Since we started to incorporate pattern-based classification into our practice, it is essential that we present data that represent our population in Thailand to inform both clinicians and patients about the implications of pattern-based diagnosis.

Age at presentation, FIGO stage, menopausal status, and tumor histology were not correlated with the tumor pattern, which was consistent with published studies[10-13]. Most of our tumors were stage I likely because we only included cases that underwent surgery and lymphadenectomy. Advanced-stage patients usually proceed with chemotherapy and radiation treatment; thus, most advanced-stage patients were excluded from our study. The proportions of LVSI and lymph node metastasis in our population were mostly comparable with published studies[6, 10-17], as we reported that pattern A was not associated with lymph node metastasis, while pattern B and C tumors were associated with LVSI and lymph node metastasis, with the highest percentage seen in pattern C.

In the analysis of recurrence and survival, patients with pattern C showed a decreased disease-free and disease-specific survival in the univariate analysis. However, after adjustment for multiple clinicopathological variables, no significant association was observed between tumor patterns and survival outcomes. These may be attributed by pattern C tumors were associated with more tumor depth and width and were associated with higher FIGO stage.

Since pattern-based classification of cervical adenocarcinoma was developed, pattern A tumors have been reported to have no risk of lymph node metastasis or recurrence. However, there were studies using pattern-based that described pattern A tumor with ovarian and lung metastasis. Feinberg[22] described 8 cervical adenocarcinoma cases with pattern A that were associated with ovarian metastases (3 cases with usual type and 5 cases with intestinal type), with two of these patients also presented with lung metastasis. Zhang[23] described 4 cases of cervical adenocarcinoma with villoglandular variants, which corresponded with pattern A in Silva system, with 1 case with lung metastasis. Furthermore, there were case reports and case series of endocervical adenocarcinoma in situ (AIS) with ovarian metastasis[24-27] and AIS with ovarian and lung metastasis[28] that were published before the proposed pattern-based classification. The proposed mechanism of how the AIS metastasized was spread of neoplastic epithelium from the endocervix to the upper genital tract, transported through endometrium, then through fallopian tubes and to ovaries[24], with distant metastasis via lymphatics and/or blood vessels (seed and soil hypothesis)[28 - 29]. Since by definition, pattern A endocervical adenocarcinoma possess non-destructive stromal invasion and the interobserver variability in distinguishing AIS from pattern A endocervical adenocarcinoma was fair to poor (kappa value of 0.23)[10]. It is possible that some of these tumors could be classified as pattern A endocervical adenocarcinoma if the cases were to be reviewed and classified according to pattern-based classification. In our cases, she was present with distant metastasis (lung) without evidence of ovarian metastasis. One of the possibilities is that the disease is dormant in the mucosa of the fallopian tubes and ovaries, then metastases to the lung via lymphatics and/or blood vessels.

Most of our cases were the usual type, and only five cases (5.1%) were mucinous variants. Two cases were classified as pattern A, and three cases were classified as pattern C. While some studies[10] concluded that most mucinous variant tumors were classified as pattern C, our data generally concurred with Stolnicuin[17] in that the pattern distribution in the mucinous variant is not different from other HPV-associated tumors.

One strength of our study is that we included patients with pelvic lymph node for pathological evaluation (e.g., we excluded a case of biopsy with LEEP/conization) and all of the slides were reviewed independently by the gynecologic pathologists. Another strength is since this was study from a single tertiary hospital, patients had a relatively long follow-up time, and most of our medical and pathology records are available. Our study reported less than a 100% 5-year disease-free survival in a cohort of patients with pattern A tumors. The limitation of our study is that the histologic type of most of our tumors was the usual type and that our study was a retrospective study.

Conclusion

In conclusion, the incorporation of pattern-based classification in pathology reports is beneficial for lymph node dissection. Whereas the association with disease-specific survival and disease-free survival are significantly associated with FIGO stage II and lymph node status. Patients with pattern A tumors can be managed more conservatively and lymphadenectomy is not required. However, follow-up with pelvic examination and imaging is recommended in patients with pattern A tumors to detect possible recurrence disease. Patients with pattern B and C tumors should be candidates for more aggressive treatment and can be candidates for lymphadenectomy or sentinel lymph node mapping and need closed follow-up as clinically indicated.

Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

The Association Between Low Pregnancy-Associated Plasma Protein-A levels and Adverse Pregnancy Outcomes

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ABSTRACT

Objective: The primary objective was to evaluate the association between low pregnancy-associated plasma protein-A (PAPP-A) levels and preterm birth. The secondary objectives included assessing the relationship between low PAPP-A levels and other adverse pregnancy outcomes, as well as analyzing factors affecting PAPP-A levels.

Materials and Methods: Medical records of all women with singleton pregnancies undergoing the combined first trimester Down syndrome screening test between 11-14 weeks of gestation from January 2014 to December 2023 were reviewed. Baseline characteristics and pregnancy outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, preterm delivery, and fetal growth restriction were compared between women with normal and low PAPP-A levels (< 0.4 multiples of median (MoM)).

Results: A total number of 2,023 women were enrolled, of whom 120 (5.9%) had low PAPP-A levels. Higher body mass index, multiparity, diabetes mellitus and hypertension negatively influenced PAPP-A levels. Women with low PAPP-A levels had significantly higher rates of preterm birth (15.8% vs 7.2%), gestational hypertension (12.5% vs 5.3%), and fetal growth restriction (10.8% vs 3.7%). At the 0.4 MoM cutoff, the sensitivity, specificity, NPV, and PPV for predicting preterm birth were 12.18%, 94.64%, 92.72%, and 16.10%, respectively. The area under the receiver operative characteristic curve was 0.597 for preterm birth, 0.578 for gestational hypertension, and 0.585 for fetal growth, respectively.

Conclusion: Low PAPP-A levels were significantly associated with preterm birth, gestational hypertension, and fetal growth restriction. However, the overall predictive performance was limited so PAPP-A should not be used as the sole indicator for clinical decision-making.

Keywords: pregnancy-associated plasma protein-A, PAPP-A, adverse pregnancy outcomes, preterm delivery.

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ความสัมพันธ์ระหว่างระดับ pregnancy-associated plasma protein-A ที่ต่ำกับผลลัพธ์ที่ไม่พึงประสงค์ของการตั้งครรภ์

รัญชิดา แสงศิริวุฒิ , เพียงบุหลัน ยาปาน, ตวงสิทธ์ วัฒกนารา, สุพิชญา สุรเสรีวงษ์, ธนาภา เรขาวศิน พินนิงตัน

บทคัดย่อ

วัตถุประสงค์*: วัตถุประสงค์หลักของการศึกษานี้คือเพื่อประเมินความสัมพันธ์ระหว่างระดับ pregnancy-associated plasma protein-A (PAPP-A) ที่ต่ำกับการคลอดก่อนกำหนด ส่วนวัตถุประสงค์รอง ได้แก่ การศึกษาความสัมพันธ์ระหว่างระดับ PAPP-A ที่ต่ำกับภาวะแทรกซ้อนอื่น ๆ ในระหว่างตั้งครรภ์ และวิเคราะห์ปัจจัยที่มีผลต่อระดับ PAPP-A*

วัสดุและวิธีการ*: มีการทบทวนข้อมูลเวชระเบียนของหญิงตั้งครรภ์ที่มีครรภ์เดี่ยวซึ่งเข้ารับการตรวจคัดกรองดาวน์ซินโดรมไตรมาสแรกแบบรวม (combined first-trimester screening) ระหว่างอายุครรภ์ 11–14 สัปดาห์ ตั้งแต่เดือนมกราคม พ.ศ. 2557 ถึงธันวาคม พ.ศ. 2566 โดยเปรียบเทียบลักษณะพื้นฐานและผลลัพธ์ของการตั้งครรภ์ เช่น การแท้ง การเสียชีวิตของทารกในครรภ์ เบาหวานขณะตั้งครรภ์ ความดันโลหิตสูงขณะตั้งครรภ์ ภาวะครรภ์เป็นพิษ การคลอดก่อนกำหนด และการเจริญเติบโตช้าของทารกในครรภ์ ระหว่างกลุ่มที่มีระดับ PAPP-A ต่ำ (< 0.4 multiples of median (MoM)) และ ระดับปกติ*

ผลการศึกษา*: มีหญิงตั้งครรภ์จำนวนทั้งสิ้น 2,023 รายเข้าร่วมการศึกษา พบว่า ดัชนีมวลกายสูง การตั้งครรภ์หลายครั้ง เบาหวาน และความดันโลหิตสูง มีความสัมพันธ์กับระดับ PAPP-A ที่ลดลงอย่างมีนัยสำคัญ หญิงที่มีระดับ PAPP-A ต่ำมีอัตราการคลอดก่อนกำหนด (ร้อยละ 15.8 เทียบกับร้อยละ 7.2) การเกิดความดันโลหิตสูงขณะตั้งครรภ์ (ร้อยละ 12.5 เทียบกับร้อยละ 5.3) และการเจริญเติบโตช้าของทารกในครรภ์ (ร้อยละ 10.8 เทียบกับร้อยละ 3.7) สูงกว่าอย่างมีนัยสำคัญ สำหรับค่า cutoff ที่ 0.4 MoM ค่าความไว ความจำเพาะ ค่าทำนายเมื่อผลเป็นลบ และค่าทำนายเมื่อผลเป็นบวกในการทำนายการคลอดก่อนกำหนดอยู่ที่ร้อยละ 12.18, 94.64, 92.72 และ 16.10 ตามลำดับ โดยค่า area under the receiver operative characteristic สำหรับการคลอดก่อนกำหนด ความดันโลหิตสูง และการเจริญเติบโตช้าของทารกในครรภ์ เท่ากับ 0.597, 0.578 และ 0.585 ตามลำดับ*

สรุป*: ระดับ PAPP-A ที่ต่ำมีความสัมพันธ์กับการคลอดก่อนกำหนด ความดันโลหิตสูงขณะตั้งครรภ์ และการเจริญเติบโตช้าของทารกในครรภ์อย่างมีนัยสำคัญ อย่างไรก็ตาม เนื่องจากมีประสิทธิภาพในการทำนายต่ำ PAPP-A จึงไม่ควรใช้เป็นเครื่องมือเดียวในการตัดสินใจทางคลินิก*

คำสำคัญ*: Pregnancy-Associated Plasma Protein-A, PAPP-A, ภาวะแทรกซ้อนในระหว่างตั้งครรภ์, การคลอดก่อนกำหนดกำหนด*

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) is a large glycoprotein produced by the syncytiotrophoblast and decidua and released into maternal blood circulation immediately after implantation. Its concentration increases steadily throughout gestation, reaching a peak at term[1, 2]. PAPP-A plays a crucial role in breaking down insulin-like growth factor binding protein (IGFBP), thereby releasing insulin-like growth factors (IGFs), which are essential for placental and fetal growth since IGF promotes trophoblast invasion and enhances glucose and amino acid uptake[3]. If this process occurs abnormally, it is associated with miscarriage, FGR, pregnancy-induced hypertension, stillbirth, preterm birth, and cesarean section due to either fetal or maternal compromise[4]. Impaired syncytiotrophoblasts function or reduced placental volume can lead to decreased PAPP-A production[5, 6]; therefore, low PAPP-A levels may indicate compromised placental function as low PAPP-A level will be inadequate to cleave IGF, then IGF will remain in an inactive bound form causing poor fetal and placental growth ending up with adverse pregnancy outcomes[4, 7].

Numerous studies have reported an association between low PAPP-A levels and adverse pregnancy outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, fetal growth restriction, and preterm birth[4, 8-34]. However, the definitions of low PAPP-A levels vary across these studies, with cutoff points ranging from 0.39 to 0.73 multiples of median (MoM), limiting the consistency and applicability of the finding in clinical practice.

Moreover, PAPP-A levels are influenced by several factors, such as maternal weight, ethnicity, smoking status, diabetes mellitus, and method of conception[35-37], further complicating their universal application. Previous studies have shown that PAPP-A levels are generally higher in pregnant Asian women compared to Western women[38-42]. Moreover, even within the same ethnic group, regional variation exists. For example, PAPP-A levels among pregnant women in northern Thailand were found to differ from those in the southern region[40-42].

Given these inconsistencies, this study was conducted to evaluate the association between low PAPP-A levels and poor pregnancy outcomes in our population. The primary objective was to investigate the relationship between low PAPP-A levels and the risk of preterm birth since it has been a major problem causing neonatal morbidity and mortality in our population for decades. Secondary objectives included examining associations between low PAPP-A levels and other adverse outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, and fetal growth restriction, as well as identifying factors influencing PAPP-A levels.

Materials and methods

Following approval from the Siriraj Institutional Review Board (SIRB 754/2567), this retrospective diagnostic study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Electronic medical records were reviewed for all women with singleton pregnancies undergoing the combined first trimester Down syndrome screening test between 11 and 14 weeks of gestation, from January 2014 to December 2023. Inclusion criteria required complete medical data, including age, body mass index (BMI), gestational age, gravida, ethnicity, smoking status, mode of conception, underlying medical conditions, PAPP-A levels (expressed as MoM), and obstetric outcomes. For participants who gave birth elsewhere, obstetric outcomes were obtained via telephone follow-up. Pregnant women whose birth outcomes could not be followed-up were excluded from the study. PAPP-A measurements were performed in batches using a commercial kit for an automated assay (BRAHMS PAPP-A KRYPTOR; ThermoFisher Scientific, Hennigsdorf, Germany), which was a homogeneous immunoassay (sandwich enzyme-linked immunosorbent assay (ELISA) principle using time resolved amplified cryptate emission

(TRACE) technology. The intra-assay and inter-assay coefficient variations were less than 10% and 12%, respectively.

The sample size was calculated based on a study by Shah et al[14], which evaluated the relationship between low PAPP-A levels and pregnancy complications in India. In that study, preterm birth was 25% in the low PAPP-A group compared to 14% in the normal PAPP-A group. Using a 2-sided type I error of 0.05, 80% power, percent preterm in the low and normal PAPP-A of 25% and 15% respectively and n2 (normal PAPP-A): n1 (low PAPP-A) = 15:1 (based on our data), sample size n1: n2 of 123: 1,845 (total = 1,968) was required. Therefore, retrospective data of about 2,000 subjects with PAPP-A were studied.

Gestational age was determined based on a certain last menstrual period in women with regular cycles, if consistent with first-trimester ultrasound findings. If not, gestational age was based solely on the first-trimester ultrasound performed before 14 weeks of gestation. Maternal medical conditions of interest included diabetes mellitus, chronic hypertension, systemic lupus erythematosus, and antiphospholipid syndrome. The obstetric outcomes assessed were miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, and fetal growth restriction, and preterm birth.

Miscarriage was defined as spontaneous pregnancy loss before 24 weeks of gestation[43]. Stillbirth was defined as fetal death at or beyond 20 weeks of gestation[44]. Gestational diabetes mellitus was diagnosed using either the one-step 2-hour 75-gram oral glucose tolerance test (OGTT) based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[45], or the two-step method recommended by the American College of Obstetricians and Gynecologists (ACOG)[46], which includes a 50-gram, 1-hour glucose challenge test followed by a 100-gram, 3-hour OGTT for values ≥ 140 mg/dL. Gestational hypertension was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured on two occasions at least four hours apart, arising after 20 weeks of gestation without proteinuria[47]. Preeclampsia was diagnosed in women meeting the criteria for gestational hypertension in addition to one or more of the following: proteinuria (urine dipstick ≥ 2+, protein-to-creatinine ratio ≥ 0.3, or 24-hour urine protein ≥ 300 mg), thrombocytopenia (platelet count < 100,000/μL), elevated liver enzymes (transaminases > 2 times the upper normal limit), new-onset renal insufficiency (serum creatinine > 1.1 mg/dL or doubling the baseline), pulmonary edema, or new-onset cerebral or visual disturbances[47]. Fetal growth restriction was defined as an estimated fetal weight below the 10th percentile[48]. Preterm birth was defined as delivery before 37 weeks of gestation whereas early preterm birth was defined as delivery before 34 weeks of gestation[49].

Regarding PAPP-A categorization, a cutoff value of 0.4 MoM was used, in accordance with most previous studies[9, 10, 13, 17, 23, 26, 27, 29], however, various cutoff points would also be studied. Women with serum PAPP-A levels < 0.4 MoM served as the case group, while those with levels ≥ 0.4 MoM served as the control group.

Statistical analysis

Descriptive statistics were presented as appropriate, including n (%), mean ± standard deviation (SD), and median with interquartile range (IQR). The chi-square test was used to compare categorical variables between the low and normal PAPP-A groups. A p value of less than 0.05 was considered statistically significant. The predictive performance of various PAPP-A cutoff levels were evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both primary and secondary outcomes. Spearman correlation and receiver operating characteristic (ROC) curve analyses were used to assess relationships between independent variables. The area under the ROC curve (AUROC) was interpreted using standard academic benchmarks: 0.5 to 0.6 = fail, 0.6 to 0.7 = poor, 0.7 to 0.8 = fair, 0.8 to 0.9 = good, 0.9 to 1.0 = excellent predictive ability[50]. All statistical analyses were performed using SPSS software, version 29.0.2.0 (IBM Corp., Armonk, NY, USA).

Results

Among 2,023 pregnant women who underwent first trimester Down syndrome screening, 120 (5.9%) were found to have low PAPP-A levels. PAPP-A MoM interpretation was unavailable in 12 cases (Fig. 1). The incidence of preterm delivery was notably higher in the low PAPP-A group compared to the normal PAPP-A group (15.8 % vs 7.2 %).

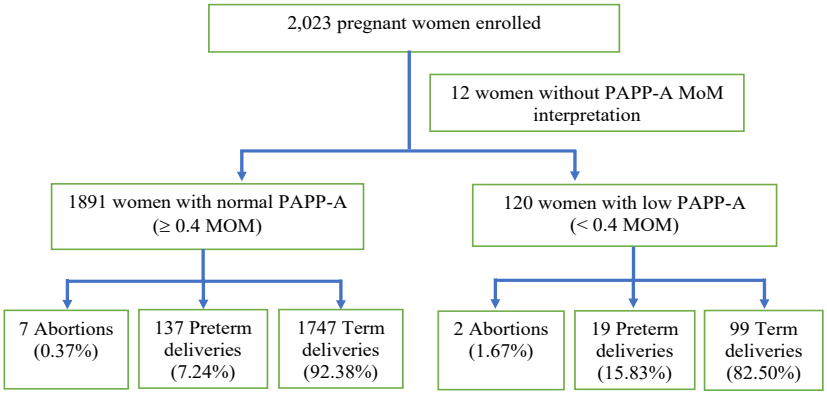

Fig. 1. Flow diagram of participants with and without preterm delivery

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median

As shown in Table 1, baseline characteristics were generally similar between the two groups, with notable differences: women in the low PAPP-A group had higher BMI (26.1 kg/m^2 vs 23.1 kg/m^2), lower mean gestational age at delivery (37.2 weeks vs 38.1 weeks), and higher rates of hypertension (5.8% vs 1.8%), and diabetes mellitus (5.8% vs 1.2%). Factors associated with reduced PAPP-A levels included higher BMI, multiparity, diabetes mellitus, and hypertension (Table 2).

Table 1. Baseline characteristics of the participants (n = 2,023).

Baseline characteristics	PAPP-A group: mean ± SD (min-max)			p value
	Total (n = 2,023)	Normal (n = 1,891)	Low (n = 120)	
Age (year)	29.9 ± 4.6 (18 - 44)	29.9 ± 4.6	30.0 ± 4.5	0.760
BMI (kg/m^2)	23.3 ± 4.8 (14.4 - 52.1)	23.1 ± 4.7	26.1 ± 6.7	< 0.001
Gestational age (weeks)	38.1 ± 2.0 (14 - 41)	38.1 ± 1.9	37.2 ± 3.0	0.001
Gravida, n (%)				0.189
Nulliparity	927 (45.8)	873 (46.2)	48 (40.0)	
Multiparity	1,096 (54.2)	1,018 (53.8)	72 (60.0)	
Southeast Asian, n (%)	2,023 (100)	1,891 (100)	120 (100)	1.000
Smoking, n (%)	6 (0.3)	5 (0.3)	1 (0.8)	0.309
Mode of conception, n (%)				1.000
Natural	1,999 (98.8)	1,868 (98.8)	119 (99.2)	
ART	24 (1.2)	23 (1.2)	1 (0.8)	
Medical conditions, n (%)				
Hypertension	41 (2.0)	34 (1.8)	7 (5.8)	0.009
Pregestational DM	30 (1.5)	23 (1.2)	7 (5.8)	0.001
SLE	10 (0.5)	10 (0.5)	0	1.000

PAPP-A: pregnancy-associated plasma protein-A, SD: standard deviation, BMI: body mass index, ART: assisted reproductive technology, SLE: systemic lupus erythematosus, DM: diabetes mellitus

Table 2. Effects of baseline characteristics on PAPP-A MoM in 2011 subjects.

Baseline characteristics	n	PAPP-A MoM: Mean ± SD	p value
BMI (kg/m^2)			< 0.001
• < 18.50	266	1.27 ± 0.61	
• 18.50 - 24.99	1,160	1.13 ± 0.59	
• 25 - 29.99	393	0.92 ± 0.47	
• ≥ 30	192	0.81 ± 0.43	
Gravida			0.010
• Nulliparity	921	1.11 ± 0.57	
• Multiparity	1,090	1.04 ± 0.57	
Mode of conception			0.108
• Natural	1,987	1.07 ± 0.57	
• ART	24	1.26 ± 0.77	
Smoking			0.431
• No	2,005	1.07 ± 0.57	
• Yes	6	0.89 ± 0.41	
Hypertension			0.025
• No	1,970	1.08 ± 0.57	
• Yes	41	0.88 ± 0.59	
DM			< 0.001
• No	1,981	1.08 ± 0.57	
• Yes	30	0.66 ± 0.48	
SLE			0.040
• No	2,001	1.07 ± 0.57	
• Yes	10	1.45 ± 0.69	

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median, SD: standard deviation, BMI: body mass index, ART: assisted reproductive technology, DM: diabetes mellitus, SLE: systemic lupus erythematosus

Regarding adverse pregnancy outcomes (Table 3), women with low PAPP-A levels had significantly higher rates of preterm birth (15.8% vs 7.2%), gestational hypertension, and fetal growth restriction (10.8% vs 3.7%). Other adverse pregnancy outcomes were more frequent in the low PAPP-A group but did not reach statistical significance.

Table 3: Adverse pregnancy outcomes in patients with normal versus low PAPP-A levels (< 0.4 MoM).

Pregnancy outcomes	PAPP-A group: Number (%)		RR (95% CI)	p value
	Normal (n = 1891)	Low (n = 120)		
Outcome				< 0.001
Abortion	7 (0.4)	2 (1.7)	4.50 (0.95, 21.44)	
Preterm birth	137 (7.2)	19 (15.8)	2.19 (1.40, 3.40)	
Early preterm (GA < 34)	22 (1.2)	6 (5.0)	4.30 (1.78, 10.40)	
Late preterm (GA ≥ 34)	115 (6.1)	13 (10.8)	1.78 (1.04, 3.07)	
Term	1747 (92.4)	99 (82.5)	0.89 (0.82, 0.97)	
Stillbirth	7 (0.4)	2 (1.7)	4.50 (0.95, 21.44)	0.097
Gestational diabetes mellitus	298 (15.8)	26 (21.7)	1.37 (0.96, 1.96)	0.088
Gestational hypertension	101 (5.3)	15 (12.5)	2.34 (1.41, 3.90)	0.001
Preeclampsia	16 (0.8)	2 (1.7)	1.97 (0.46, 8.47)	0.292
Fetal growth restriction	70 (3.7)	13 (10.8)	2.93 (1.67, 5.14)	< 0.001

MoM: multiples of median, PAPP-A: pregnancy-associated plasma protein-A, RR: relative risk, CI: confidence interval, GA: gestational age

Table 4 presents the diagnostic performance of various PAPP-A cutoff points for predicting preterm birth, gestational hypertension, and fetal growth restriction. Using the 0.4 MoM threshold, the sensitivity, specificity, NPV, and PPV for predicting preterm birth were 12.18%, 94.64%, 92.72%, and 16.10%, respectively. Higher cutoff values led to increased sensitivity, while specificity and PPV declined, while NPV remained relatively stable. Among all adverse pregnancy outcomes, fetal growth restriction showed the highest NPV and lowest PPV, followed by gestational hypertension and preterm birth. Nevertheless, Youden's index was notably low among all cutoff values.

Table 4. Diagnostic performance of PAPP-A MoM in predicting preterm birth, gestational hypertension, and fetal growth restriction.

Pregnancy outcomes	PAPP-A (MoM)	Percent				
		Sensitivity	Specificity	Youden's index	NPV	PPV
Preterm birth	< 0.4	12.2	94.6	6.8	92.7	16.1
	< 0.5	19.9	88.9	8.8	92.9	13.2
	< 0.6	26.9	82.2	9.1	93.0	11.4
	< 0.7	38.5	74.3	12.8	93.5	11.2
	< 0.8	46.2	65.3	11.5	93.5	10.1
	< 0.9	55.8	56.8	12.6	93.8	9.8
	< 1.0	64.1	48.8	12.9	94.1	9.6
Gestational	< 0.4	12.9	94.5	7.4	94.7	12.5
hypertension	< 0.5	18.1	88.6	6.7	94.6	8.9
	< 0.6	28.4	82.0	10.4	94.9	8.8
	< 0.7	36.2	73.7	9.9	95.0	7.8
	< 0.8	44.8	64.8	9.6	95.0	7.2
	< 0.9	55.2	56.4	11.6	95.4	7.2
	< 1.0	62.1	48.2	10.3	95.4	6.8
Fetal growth	< 0.4	15.7	94.5	10.2	96.3	10.8
restriction	< 0.5	21.7	88.6	10.3	96.3	7.6
	< 0.6	26.5	81.7	8.2	96.3	5.9
	< 0.7	33.7	73.4	7.1	96.3	5.2
	< 0.8	43.4	64.6	8.0	96.4	5.0
	< 0.9	53.0	56.1	9.1	96.5	4.9
	< 1.0	59.0	47.9	6.9	96.5	4.7

PAPP-A: pregnancy-associated plasma protein-A, NPV: negative predictive value, PPV: positive predictive value

The ROC curves for predicting preterm birth, gestational hypertension and fetal growth restriction using PAPP-A levels are shown in Figure 2. The AUROC values were 0.597 for preterm birth, 0.578 for gestational hypertension, and 0.585 for fetal growth restriction, respectively.

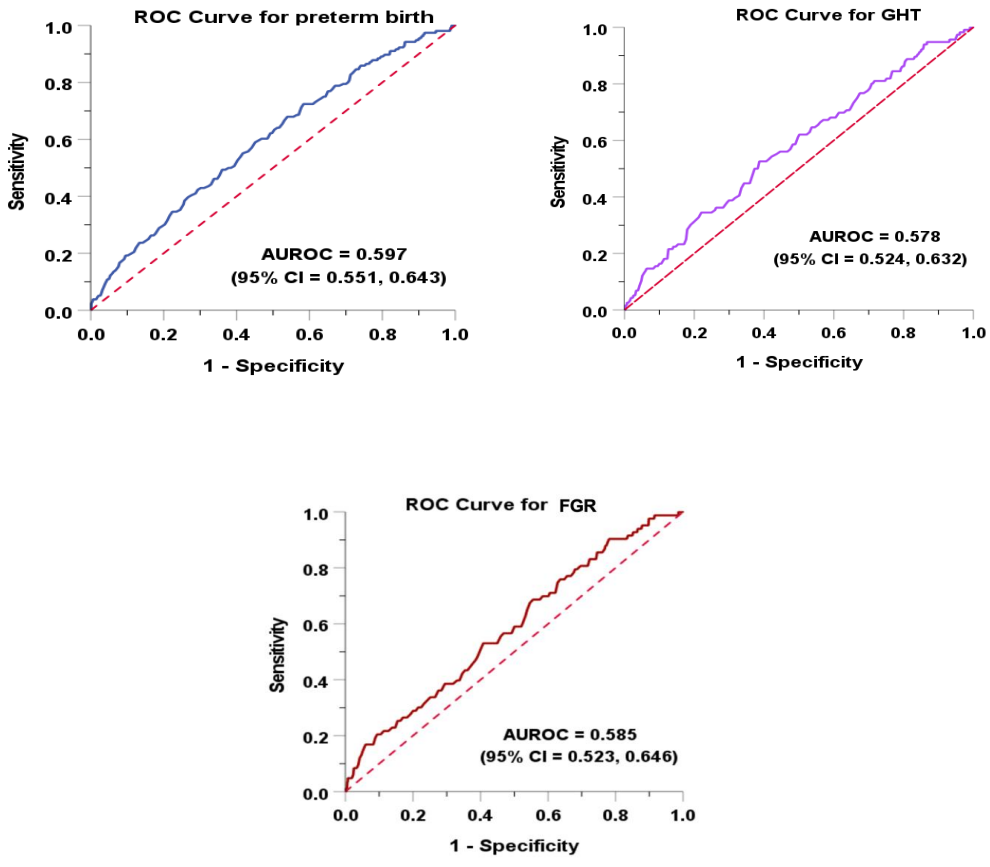

Fig. 2. Receiver operating characteristic (ROC) curves for low PAPP-A (< 0.4 MoM) in predicting preterm birth, gestational hypertension, and fetal growth restriction

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median

Discussion

This study demonstrated a significant association between low PAPP-A levels (< 0.4 MoM) and adverse pregnancy outcomes, specifically preterm birth, gestational hypertension, and fetal growth restriction. There was no obvious optimal cutoff point to define low PAPP-A levels in this study.

PAPP-A is an IGFBP protease leading to the release of IGF which is paramount in fetal growth[51] through the process of trophoblast invasion, regulation of glucose and amino acid transport in chorionic villi[52]. If this process occurs abnormally, it is associated with miscarriage, fetal growth restriction, pregnancy-induced hypertension, stillbirth, preterm birth, and cesarean section due to either fetal or maternal compromise[4]. Consequently, low PAPP-A level will be inadequate to cleave IGF, then IGF will remain in an inactive bound form causing poor fetal and placental growth ending up with adverse pregnancy outcomes[4, 7].

Pregnant women in the low PAPP-A group tended to have a higher BMI, consistent with findings from previous studies[35, 37]. Lower PAPP-A levels observed in earlier gestational ages were also in line with studies showing the trend of rising PAPP-A levels throughout pregnancy[1, 2]. Additionally, medical conditions, such as diabetes mellitus and hypertension were associated with reduced PAPP-A levels, likely reflecting poor placental growth and lower PAPP-A levels. These associations, particularly the link

between diabetes mellitus and PAPP-A levels has been reported in prior research[37]. Similarly, smokers and multiparous women had lower PAPP-A levels, as shown in previous studies[37]; however, the small number of smokers in our cohort may have limited statistical significance.

In contrast to earlier studies, we found no significant association between mode of conception and PAPP-A levels, which was different from a previous study that showed that women who conceived with assisted reproductive technology (ART) had lower PAPP-A levels, with increases observed in the third trimester (IVF pregnancies)[37]. This could be due to a small number of ART cases leading to inadequate power for detection.

Regarding adverse pregnancy outcomes, low PAPP-A levels were strongly associated with preterm birth, aligning with previous studies that used cutoff values ranging from 0.35-0.59 MoM[4, 10, 11, 14-19, 25-27, 29]. Notably, this association remained consistent when only studies using the 0.4 MoM threshold were considered. Likewise, increased incidences of gestational hypertension and fetal growth restriction in the low PAPP-A group were consistent with prior findings[4, 11, 13, 14, 16, 17, 24, 25, 28, 29]. However, some studies found a higher occurrence of gestational hypertension in women with low PAPP-A without reaching statistical significance[12, 23, 31, 32], which may be due to differing cutoff definitions or the grouping of gestational hypertension and preeclampsia into a single outcome. Although miscarriage was more frequent among women with low PAPP-A levels in our study, the association was not statistically significant, in line with findings reported of another study[23]. This contrasted with the results of Movahedi et al[8], who reported a significant link between low PAPP-A levels and miscarriage, possibly due to a larger proportion of miscarriages in their sample. Lata et al[25] conversely found a higher rate of miscarriage in normal PAPP-A level group, however, there was only one miscarriage case in that group and the definition of miscarriage was based on ACOG guideline using a diagnostic cutoff point of 24 weeks' gestation. A similar trend was observed in stillbirths: while rates were higher in the low PAPP-A group, the difference was not statistically significant, echoing the results of previous studies[14, 29]. However, a contrasting outcome was reported in another Thai study, where a stronger association was likely influenced by a higher incidence of stillbirth in their population[11].

Our study found no significant association between low PAPP-A levels and gestational diabetes mellitus, despite a higher incidence of adverse outcomes — consistent with prior studies[14, 25]. This contrasted with previous studies[30-34] that demonstrated a significant link possibly due to the inhibitory effect of low PAPP-A on IGF-1, impairing glucose homeostasis and increasing insulin resistance. However, these studies used a much higher cutoff point of 0.995 MoM. Preeclampsia was observed approximately twice as common in the low PAPP-A group, though the difference did not reach statistical significance which could be explained by a small number of cases due to insufficient sample size. Similar findings have been reported in other studies as well[23, 28, 33], while several other studies found a significant association[8, 9, 11-13, 16, 17, 20, 29].

This study clearly demonstrated that all obstetric complications were higher in women with low PAPP-A levels, even when statistical significance was not achieved in some cases, likely due to limited sample size for certain outcomes.

When evaluating the predictive performance of low PAPP-A levels (cutoff 0.4 MoM), the test showed poor accuracy for predicting preterm birth, gestational hypertension, and fetal growth restriction. This aligned with a previous study[16], which reported AUROC values around 0.6 for both preterm delivery and small-for-gestational-age (SGA) infants, although SGA was defined as weight < 5th percentile which was lower than in our study. Likewise, Goetzinger et al reported an AUROC of 0.63, using a cutoff of 0.59 MoM for predicting preterm birth before 35 weeks. Dane et al[18], however, reported better predictive performance (AUROC = 0.74) for preterm delivery using a lower cutoff point of 0.35 MoM and defining preterm birth

as delivery before 34 weeks.

Given that PAPP-A levels tend to be higher among Asian populations compared to Caucasians, our study also explored alternative cutoff points to determine whether higher cutoff ones would be of value. Although previous Thai studies used 0.53 MoM as the threshold[11, 15], different PAPP-A values were observed among different regions[40-42]. Nonetheless, there was no obvious optimal cutoff point for defining low PAPP-A levels in predicting adverse pregnancy outcomes in this study based on Youden's index.

A key strength of this retrospective study was the large and adequate sample size, allowing for robust analysis of the primary outcome. In addition, there was no missing data, making the conclusion reliable. To our knowledge, this is the first study to evaluate various higher PAPP-A cutoff points to identify the optimal threshold in a Thai population. However, some limitations were observed. The sample size may have been insufficient to detect significant associations between low PAPP-A level and adverse pregnancy outcomes. Additionally, women with low PAPP-A levels in this study were not classified by the presence or absence of known risk factors for preterm birth, which may have influenced the results. Preterm birth cases were not categorized into spontaneous and indicated as well. Also, a small number of women (7.3%) were followed-up by a telephone interview so the obtained adverse pregnancy outcomes especially pregnancy-induced hypertension may be less reliable giving rise to lower-than-expected prevalence of preeclampsia in this study. Moreover, gestational diabetes mellitus diagnosis was based on two diagnostic criteria which might affect the prevalence rate of both groups in our study.

Since this study is based on a PAPP-A level serum marker, its use in clinical management is limited since there are a lot of other risk factors for adverse pregnancy outcomes. Therefore, it cannot replace current screening tools such as those used for preeclampsia risk. However, PAPP-A could serve as an early marker for guiding further follow-up for preterm birth, gestational hypertension, and fetal growth restriction, especially among those without other risk factors for developing adverse outcomes. Future research should stratify women by risk profile to accurately assess independent impact of low PAPP-A on specific pregnancy complications.

Conclusion

Low PAPP-A levels were associated with an increased risk of preterm birth, gestational hypertension, and fetal growth restriction. However, the overall predictive performance was limited so PAPP-A should not be used as the sole indicator for clinical decision-making.

Potential conflicts of interest

The authors declare no conflicts of interest.

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