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EDITORIAL

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

Vorapong Phupong, M.D., FRTCOG.*

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

This fourth issue of Thai Journal of Obstetrics and Gynaecology 2025 contains many interesting articles. The special article is "Hyperemesis gravidrum: updated review". The authors reviewed the diagnostic criteria, etiology and risk factors, investigation and treatment[1].

This issue also contains seven original articles and one case report. Mahachiraphat et al performed a cross-sectional study to investigate the correlation between serum vitamin D levels and myoma uteri volume in Thai women and found serum vitamin D levels were weak and inversely correlated to the myoma uteri volume[2].

Noknu et al performed a retrospective cohort study involving singleton pregnancies with late preterm labor to develop and internally validate a predictive model for estimating the likelihood of delivery within 7 days of the onset of spontaneous late preterm labor. They found this model high predictive performance[3].

Udompornthanakij et al performed a prospective observational study to evaluate the maternal oxygen saturation at the 5th minute, as measured by pulse oximetry and non-stress test results in pregnant women when they were not wearing and wearing a face mask. They found the mean maternal oxygen saturation and maternal diastolic blood pressure were significantly lower at the 5th minute of monitoring the participants when wearing a face mask than at the 5th minute when not wearing a face mask, but the trend was no difference when monitoring for a longer time[4].

Suriyachan et al performed a quasi-experimental study to assess the impact of a video on pertussis vaccination intentions among pregnant women and identify factors influencing their decision-making. They found viewing the video increased vaccination intentions by 42%, particularly among women who were initially uncertain about vaccination[5].

Manaying et al performed a randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of local cervical lidocaine spray with intravenous meperidine for pain relief during the manual vacuum aspiration (MVA) procedure compared to a local placebo spray with intravenous meperidine. The result showed that lidocaine spray could effectively reduce the pain at immediately post MVA without any serious side effects[6].

Thitipatlertdech et al performed a study to evaluate human sperm vitality after cryopreservation by comparing a cryopreservation medium with and without the addition of autologous platelet-rich plasma (aPRP). They found the supplementation of cryopreservation media with aPRP significantly increased sperm survival rates after the freeze-thaw process[7].

Tinsatid et al performed a retrospective study to evaluate 5-year overall survival (OS), 5-year disease-free survival (DFS), recurrent rate and identified prognostic clinicopathological factors of patients with clinically early-

stage cervical cancer treated with primary surgery. The results revealed that the 5-year OS and DFS of clinically early-stage cervical cancer were 85.3% and 84.0%, respectively. Adjuvant postoperative radiotherapy was the protective factor for recurrence[8].

Regarding a case report, Glenardi et al reported a rare case of ruptured primary ovarian pregnancy in woman presented with severe lower abdominal pain and amenorrhea[9].

Finally, we are pleased to inform the Royal Thai College of Obstetricians and Gynaecologists (RTCOG) members that the ranking of Thai Journal of Obstetrics and Gynaecology (TJOG) increases from 16th percentile in year 2023 to 22nd percentile in year 2024 (164/210 journals) with CiteScore increases from 0.4 to 0.6 in Obstetrics and Gynaecology category from Scopus database. The quality of TJOG has improved. The journal editorial team would like to thank past RTCOG executive board, past editor in chief, editorial board and staff, reviewers, all members of RTCOG, and all researchers for their kind contribution and support to TJOG.

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SPECIAL ARTICLE

Hyperemesis Gravidrum: Updated review

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ABSTRACT

Nausea and vomiting (NV) are crucial problems during early pregnancy. Hyperemesis gravidarum (HG) is a severe form of NV. Generally, the diagnosis of HG is based on the severity of NV. We updated some criteria for HG diagnosis that have been proposed to help standardize HG research, the interesting treatable risk factors such as gastroesophageal reflux disease (GERD) or Helicobacter pylori (H. pylori) infection. Lastly, several treatment options are reviewed.

Keywords: nausea, vomiting, pregnancy, hyperemesis.

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Overview and definition

Nausea and vomiting (NV) are common conditions during early pregnancy. Pregnant women usually start experiencing NV before 5-6 weeks of gestation, and symptoms disappear around 12-16 weeks of gestation[1]. The prevalence of NV in pregnancy is estimated to be approximately 50-80% for nausea and 50% for vomiting and retching[2]. Hyperemesis gravidarum (HG) is a severe form of NV. It affects approximately 0.3-2% of all pregnancies[3]. HG have been positively reported to be associated with good fetal outcomes and strongly reduced the miscarriage risk[4]. However, severe and persistent HG can lead to adverse pregnancy outcome, such as intrauterine growth restriction, impaired maternal nutritional status and low fetal birth weight[4]. The diagnosis of HG is based primarily on the severity of NV during early pregnancy and its impact on the pregnant woman's metabolism. Currently, there are no universally accepted criteria for HG diagnosis. Some criteria for HG diagnosis have been proposed to help standardize HG research. The Fairweather criteria (1968) and the Windsor criteria (2021) are among the diagnostic criteria mentioned in the

literature[5].

The Fairweather criteria consist of[6]

- NV occurring more than 3 times /day, first appearing between 4 and 8 weeks of gestation.
- Weight loss.
- Ketonemia.
- Volume depletion.
- Electrolyte imbalance.

The Windsor criteria comprise[7]

- Mandatory features.
  - NV starting early in pregnancy (before a gestational age of 16 weeks), with at least one severe symptom.
  - Inability to drink or eat normally.
  - Strongly affects daily living activities.
- Contributory features
  - Signs of dehydration.

Etiology and risk factors of HG

HG is proposed to have a multifactorial etiology[5], including endocrine, gastrointestinal, metabolic, enzyme and immunologic adaptations during pregnancy[7]. Risk factors for HG include younger or older maternal age, abnormal pre-pregnancy weight (underweight or overweight), Black or Asian ethnicity, pregnancy with a female fetus, multiple gestations, history of pre-pregnancy gastroesophageal reflux disease (GERD) or Helicobacter pylori (H. pylori) infection[9]. The prevalence of H. pylori has been reported to be around 46% in pregnant women[10]. Interestingly, an association between H. pylori and several adverse pregnancy outcomes, such as low gestational weight gain, fetal growth restriction, and intrauterine fetal death, has been found[9-11]. Importantly, if HG worsens beyond the usual gestation period (later than 14 weeks) or if questionable abnormal clinical symptoms and signs are present, a differential diagnosis for other serious conditions should be considered. A malignant brain tumor in early pregnancy has also been reported as being mistaken for HG[12]. NV during pregnancy and HG must be distinguished from the following medical conditions[13-14]:

- Cerebral nervous system: cerebral hemorrhage, meningitis, subarachnoid hemorrhage and brain tumor.
- Ocular system: glaucoma.
- Otolaryngologic system: Meniere's disease, benign paroxysmal positional vertigo and vestibular neuritis.
- Cardiovascular system: angina pectoris, myocardial infarction.
- Female reproductive system: pelvic inflammatory disease, adnexal torsion.
- Gastrointestinal system: ulcer, appendicitis, gut obstruction, gastroenteritis, peritonitis, hepatitis, cholecystitis, cholangitis.
- Kidney and urinary bladder system: ureteral stone, pyelonephritis.
- Psychiatric problems: depression, migraine, bulimia.
- Miscellaneous: drug use.

Management of HG

Investigation

The proper investigation is arranged individually based on the clinical condition of each pregnant woman. Most investigations primarily aim to identify the causes of HG and assess its severity. Suggested investigations for HG are described below[15]:

- Complete blood count: to rule out infection, anemia.
- Serum urea and electrolytes (evaluate for hypo/hyperkalemia, hyponatremia, or high creatinine): to properly determine the type of intravenous fluid and electrolyte replacement, and to evaluate for acute kidney injury following dehydration.
- Blood glucose level: to exclude diabetic ketoacidosis in diabetic pregnant women.
- Obstetric ultrasonography: to assess fetal viability and exclude possible abnormal pregnancies associated with HG, such as multiple pregnancies or gestational trophoblastic disease.
- Urinalysis: to rule out infection. Assessing dehydration should be based on clinical signs and symptoms rather than the presence or absence of

ketonuria. Using ketonuria alone may be misleading in determining dehydration status[15]. Clinical signs and symptoms of dehydration include hypersalivation, weight loss, loss of daily activity performance or quality of life disturbances, etc.

● Other laboratory tests may be warranted in refractory cases, such as thyroid function tests, liver function tests, etc.

Treatment

A multi-modal approach to the treatment of HG has been reported. It can be categorized into the following groups:

● Antiemetic drugs (pharmaceutical modality): Antihistamines (H1 antagonists), including doxylamine combined with pyridoxine hydrochloride (vitamin B6), dimenhydrinate, meclizine and diphenhydramine, are used to relieve NV[16]. Some literature reviews have reported that only the delayed-release formulation of doxylamine succinate and pyridoxine hydrochloride is more effective than placebo in reducing NV[5,17]. Recent findings have highlighted a relationship between HG and growth/differentiation factor 15 (GDF15)[18]. Consequently, recent research has focused on the role of targeting GDF15 to reduce NV and HG. However, fetal safety is still not well-established. Future studies should investigate this further and explore screening methods to identify pregnant women at risk for HG who may need early intervention to improve clinical outcomes.

● Alternative non-pharmaceutical modality: Several interventions have been documented, such as herbs (ginger, chamomile), acupuncture and massage. The effectiveness of alternative non-pharmaceutical modalities is still controversial, and the mechanism of their therapeutic effects remains unclear[19-20].

● Dietary adjustment: A balanced and appropriate diet plays a crucial role in NV and HG control. It can help stabilize blood glucose levels and meet essential nutrient requirements. Previous studies have found that diets rich in complex carbohydrates, protein, and dietary patterns rich in fruits, vegetables, and essential vitamins and minerals can help relieve and support NV and HG management and reduce the risk of nutritional deficiencies in severe HG cases[21].

● Intravenous fluids: Rehydration, along with the correction of electrolyte imbalances, is very important.

Conclusion

In conclusion, HG is a potentially severe condition during pregnancy. Understanding the causes of HG and updating treatment options is essential.

Potential conflicts of interest

The authors declare no competing interests.

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GYNAECOLOGY

Correlation between Uterine Fibroid Volume and Vitamin D Level in Thai Women: A cross-sectional study

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ABSTRACT

Objectives: This study aimed to investigate the correlation between serum vitamin D levels and myoma uteri volume in Thai women.

Materials and Methods: This study enrolled ninety Thai women diagnosed with uterine leiomyoma. We used pelvic ultrasound to measure the total myoma volume and collected blood samples on the same day to assess serum vitamin D levels. The correlation between vitamin D levels and myoma uteri volume was then analyzed. We measured the myoma volume using the formula of width x length x height x 0.523. Vitamin D level was measured by electrochemiluminescence immunoassay.

Results: The median volume of myoma uteri was 24.57 cm^3 (max = 1946.03, min = 1.05). The median serum vitamin D level was 20.35 ng/mL (max = 46, min = 7.50). The study found a weak inverse correlation between serum vitamin D levels and myoma uteri volume, although the correlation coefficient indicated a low correlation (Pearson correlation coefficient, r = - 0.239; p = 0.023). The prevalence of vitamin D deficiency in Thai women in the study was 48.9%.

Conclusion: Serum vitamin D levels were weak and inversely correlated to the myoma uteri volume among Thai women.

Keywords: myoma uteri, vitamin D, vitamin D deficiency.

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ความสัมพันธ์ระหว่างปริมาตรเนื้องอกกล้ามเนื้อมดลูกและระดับวิตามินดีในหญิงไทย

กฤติภร มหาจิราภัทร์, สิตานัน เลิศศิริพาณิชย์

บทคัดย่อ

วัตถุประสงค์*: การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างระดับวิตามินดีในเลือดกับปริมาตรของ เนื้องอกมดลูกในผู้หญิงไทย*

วัสดุและวิธีการ*: การศึกษาครั้งนี้ทำการศึกษาในกลุ่มสตรีที่อยู่ในช่วงอายุ 18-50 ปี ที่มีเนื้องอกกล้ามเนื้อมดลูก ขนาดรวมกันมากกว่า 2 เซนติเมตรขึ้นไป ที่มารับการรักษาที่แผนกนรีเวช โรงพยาบาลราชวิถี ในระหว่างเดือน กรกฎาคม 2567 - กันยายน 2567 โดยการตรวจคลื่นความถี่สูงบริเวณเชิงกราน เพื่อวัดปริมาตรรวมของเนื้องอกมดลูก คำนวณจาก ความกว้าง x ความยาว x ความสูง x 0.523 และเก็บตัวอย่างเลือดในวันเดียวกัน เพื่อตรวจสอบ ระดับวิตามินดีในเลือด ระดับวิตามินดีถูกวัดโดยใช้วิธี electrochemiluminescence immunoassay จากนั้นทำการวิเคราะห์ความสัมพันธ์ระหว่างระดับวิตามินดีและปริมาตรเนื้องอกมดลูกปริมาตรของเนื้องอกมดลูก*

ผลการศึกษา*: มัธยฐานของเนื้องอกมดลูกอยู่ที่ 24.57 ลูกบาศก์เซนติเมตร (ต่ำสุด = 1.05, สูงสุด = 1946.03) : มัธยฐานของระดับวิตามินดีอยู่ที่ 20.35 นาโนกรัมต่อมิลลิลิตร (ต่ำสุด = 7.5, สูงสุด = 46) พบว่ามีความสัมพันธ์เชิงลบอย่างมีนัยสำคัญทางสถิติระหว่างระดับวิตามินดีในเลือดและปริมาตรเนื้องอกมดลูก แม้ว่าสัมประสิทธิ์สหสัมพันธ์จะแสดงถึงความสัมพันธ์ในระดับต่ำ (สัมประสิทธิ์สหสัมพันธ์เพียร์สัน, r = - 0.239; p = 0.023) นอกจากนี้พบว่าร้อยละ 48.9 ของผู้หญิงไทยในกลุ่มตัวอย่างมีภาวะขาดวิตามินดี*

สรุป*: ระดับวิตามินดีในเลือดที่ตำลงมีความสัมพันธ์เชิงผกผันเล็กน้อยกับการเพิ่มขึ้นของปริมาตรเนื้องอกมดลูกในผู้หญิงไทย*

คำสำคัญ*: เนื้องอกมดลูก, วิตามินดี, ภาวะขาดวิตามินดี*

Introduction

Uterine fibroids are the most common smooth muscle tumors of the uterus[1], with the highest prevalence found in reproductive aged women. These fibroids contribute to about 30% of hysterectomy in women aged 18-44[2]. In Thailand, 60% of women who underwent hysterectomy were diagnosed with uterine fibroids.

The prevalence of vitamin D deficiency in Thai women with uterine fibroids was 69.6%[3]. Common presenting symptoms of uterine leiomyoma are varied by size, location and type of the fibroids, which include abnormal uterine bleeding, anemia, miscarriage[4], infertility, frequent urination, difficulty in urination[5], constipation, and difficulty with bowel movements[5].

Vitamin D can be synthesized in the skin under ultraviolet B radiation. Avoiding sunlight and applying sunscreen can decrease vitamin D synthesis[6]. Other sources of vitamin D include consumption of fatty fish, eggs and milk. Vitamin D deficiency has become more prevalent, particularly in Thai women aged 25-54, with a rate of 43.1%[8]. Interestingly, vitamin D deficiency is more common among patients with uterine fibroids compared to those without[9].

Animal and human studies suggest that vitamin D can reduce the growth rate of uterine fibroids[7]. Hypothesis of vitamin D inhibitory function in fibroid growth includes suppressing of cell growth and proliferating-related genes, antiapoptotic genes, modulation of estrogen and progesterone receptors[7] and mediation of transforming growth factor beta activities of the tumor cells[9]. Despite these findings, previous studies have shown conflicting results on the correlation between fibroid volume and the severity of vitamin D deficiency. From our extensive review, there is no study on this subject in Thailand. This research aimed to explore the relationship between uterine fibroid volume and vitamin D levels in Thai women, with the secondary outcomes of exploring the severity of vitamin D level deficiency in Thai women, and to identify other personal and environmental factors that may affect uterine fibroid volume.

Materials and Methods

Thai women aged 18-50 years old who visited the Gynecology Department of Rajavithi Hospital were recruited. The study was conducted from July to September 2024. This study was approved by the Institutional Review Board of Rajavithi Hospital (EC number 67057). The trial was completed without any protocol amendments.

The inclusion criteria consisted of Thai female patients aged 18-50 years who were diagnosed with myoma uteri size greater than 2 centimeters in total by pelvic ultrasonography (combining the largest diameter of all myoma) and were willing to participate in the research. The exclusion criteria for this study included women receiving gonadotropin-releasing hormone analogues, pregnant women, postpartum or post-miscarriage women within the past 6 weeks, breastfeeding women, and postmenopausal women. Additionally, we excluded women who had previously undergone myomectomy, those who had taken vitamin D supplements within the past 6 months, and patients with chronic kidney or liver disease. Other chronic diseases affecting vitamin D metabolism, such as thyroid or parathyroid disease, also disqualified participants.

Based on a previous study, the correlation between vitamin D levels and the size of leiomyomas was used to calculate the sample size[10]. The Pearson correlation coefficient was 0.292. Using an alpha of 0.05 and a beta of 80%, a minimum sample size of 90 patients was required.

Participants in the study were enrolled by a single researcher. Personal baseline data recorded include age (years), body mass index (BMI) (kg/m^2), underlying medical conditions, current medications, smoking history, number of children, educational level, last pregnancy, and number of children. The uterine fibroids' medical history includes the year of diagnosis, family history, prior treatments, and whether the participant has previously undergone a myomectomy. Dietary and sunlight exposure were records, along with work habits, including details on sunlight exposure, use of sunscreen, clothing habits, work activities, fish consumption, egg consumption, milk consumption, current medications, and whether vitamin D or calcium supplements have been taken in the past 6 months. The hours of sun exposure were estimated using participant surveys about the direct time spent outdoors during daylight hours. Participants will undergo blood sampling to measure their serum vitamin D levels. Additionally, a pelvic ultrasound will be performed on the day of participation by qualified specialists of Gynecology Department, Rajavithi Hospital.

The Rajavithi Medical Center's blood collection room will collect blood samples using a 25-OH Vitamin D reagent kit to measure 25-hydroxyvitamin D through a quantitative chemiluminescent microparticle immunoassay (CMIA). Vitamin D deficiency is defined as levels below 20 ng/mL[11], with severe deficiency classified as below 10 ng/mL and mild to moderate deficiency ranging from 10 to 24 ng/mL[12].

A pelvic ultrasound was conducted in the ultrasound room of the Gynecology Outpatient Department at Rajavithi Hospital by 5 gynecologic staff using a Voluson S6 machine from GE Healthcare Support Services. The procedure involved transvaginal, transrectal, or transabdominal ultrasound methods. For fibroids larger than 10 cm, we used transabdominal ultrasound. For patients with no history of sexual intercourse, we used a transrectal ultrasound. The size of the uterine fibroid was calculated using the formula width × length × height × 0.523, summing the volumes of all fibroids present. There are various types depending on the location, classified according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO)[13].

Statistical analysis was performed using SPSS for Windows (version 26.0, SPSS Inc., IBM New York, USA). Descriptive statistics for basic demographic data that was categorical was reported as frequencies and percentages. For continuous data, if the data was normally distributed, it was reported as the mean and standard deviation. If the data was not normally distributed, it was reported as the median, minimum, and maximum. The significance level for all tests was set at a p value of less than 0.05. Pearson's correlation was used to assess the relationship between vitamin D levels and fibroid volume. Univariate logistic regression was applied with a significance threshold of 0.2, followed by multivariate analysis with a significance level of 0.05.

Results

The study enrolled a total of 90 patients from July to September 2024. The demographic characteristics of patients in this study are shown

in Table 1. The study involved patients with an average age of 42.2 ± 5.5 years and a mean BMI of 25.2 ± 5.2 kg/m^2. Most patients (66.7%) were nulliparous. The majority (75.6%) had no family history of uterine fibroids. Further details are summarized in Table 1.

Table 1. Baseline characteristics of the patients.

Characteristics	
Age (years), mean ± SD	42.2 ± 5.5
BMI (kg/m^2), mean ± SD	25.2 ± 5.2
Smoking, n (%)	6 (6.7)
Parity, n (%)	
0	60 (66.7)
1-2	25 (27.8)
3-4	4 (4.4)
More than 4	1 (1.1)
Pregnancy interval, n (%)	
Nulliparity	61 (67.8)
1-5 years	1 (1.1)
5-10 years	2 (2.2)
> 10 years	26 (28.9)
Family history, n (%)	
No family history	68 (75.6)
Have family history of uterine fibroid	22 (24.4)
Treatment, n (%)	
Not receiving medication	62 (68.9)
Combined oral contraception	6 (6.7)
Progestin only oral contraception	3 (3.3)
Injectable contraception	16 (17.8)
Intrauterine device	2 (2.2)
Implantation	1 (1.1)
Total myoma volume (cm^3), median (min, max)	24.57 (1.1,1946)

Data were presented as mean ± SD, median (max, min) and number (%).
SD: standard deviation, BMI: body mass index

As shown in Table 2, factors associated with vitamin D levels were assessed. Patients had an average of 1.1 ± 1.2 hours of sun exposure per day, with 74.4% reporting the use of sunscreen. The majority (75.6%) wore short sleeves, and nearly all (94.4%) worked indoors.

Table 2. Factor associated to vitamin D level.

Sun exposure (hours), mean ± SD	1.1 ± 1.2
Sunscreen application, n (%)	67 (74.4)
Cloth, n (%)	
- Wearing long sleeves	22 (24.4)
- Wearing short sleeves	68 (75.6)
Working, n (%)	
- Indoor work	85 (94.4)
- Outdoor work	5 (5.6)
Consuming fish, n (%)	
- Less than 3 times/week	66 (73.4)
- 3-5 times/week	22 (24.4)
- Eating every day	2 (2.2)
Consuming egg, n (%)	
- Less than 3 times/week	40 (44.4)
- 3-5 times/week	34 (37.8)
- Eating every day	16 (17.8)
Drinking milk, n (%)	
- Less than 3 times/week	63 (70)
- 3-5 times/week	10 (11.1)
- Eating every day	17 (18.9)

Data were presented as mean ± SD and number (%)
SD: standard deviation

Serum vitamin D levels of participants are shown in Table 3. The median serum vitamin D level was 20.35 ng/mL (range: 7.5-46), with 48.9% of participants classified as vitamin D deficient.

Table 3. Vitamin D level result (n = 90).

Vitamin D level (ng/ml), median (min, max)	20.35 (7.5, 46)
Vitamin D deficiency, n (%)	44 (48.9)
Severity, n (%)	
- Mild-Moderate	42 (46.7)
- Severe	2 (2.2)

Data were presented as median (min, max) and number (%).

Several factors demonstrate an inverse relationship between vitamin D levels and uterine myoma volume. The baseline characteristics that may influence myoma volume are summarized in Table 4. Among the studied factors, the logarithm of total vitamin D levels showed a significant association with total myoma volume in both univariate and multivariate analyses. In the multivariate model, the coefficient was -1.25, with a p value of 0.026, indicating a statistically significant relationship. Specifically, the odds ratio (OR) for log total vitamin D levels was 0.29 (95% CI 0.09–0.86), signifying a notable decrease in myoma volume with higher vitamin D levels.

Age, however, did not demonstrate a statistically significant effect on myoma volume (p = 0.342). On the other hand, multivariate analysis revealed that higher BMI was associated with larger fibroid volumes, with an OR of 1.04 (95% CI 1.00–1.07). Parity also played a significant role, as having more than three pregnancies

(compared to nulliparity), with an OR of 0.36 (95% CI 0.18–0.73).

Regarding contraceptive use, combined oral contraceptives and injectable contraceptives were significantly associated with smaller fibroid volumes. In both univariate and multivariate analyses, combined oral contraceptives, progestin-only oral contraceptives, and injectable contraceptives showed statistically significant reductions in myoma volume, with odds ratios of 0.48, 0.36, and 0.43, respectively.

Factors associated with vitamin D levels, such as smoking, sun exposure, clothing, sunscreen use, type of work, and diet, were not found to have statistically significant effects.

Table 4. Factor that may influence the logarithm of total myoma volume.

	Univariate		Multivariate		Odds ratio (95% CI)	p value
	95% CI	p value	95% CI	p value		
Interesting factor						
Log total vitamin D	-0.24, -0.18	0.023	-2.35, -0.15	0.026*	0.29 (0.09, 0.86)	0.026*
Baseline characteristic						
Age	-0.05, 0.01	0.149	-0.05, 0.02	0.342	0.98 (0.95, 1.02)	0.342
BMI	-0.01, 0.05	0.191	0.001, 0.07	0.026*	1.04 (1.00, 1.07)	0.026*
Parity						
- Nulliparity	Ref.		Ref.			
- 1-2	-0.68, 0.08	0.122	-0.60, 0.16	0.246	0.80 (0.55, 1.17)	0.246
- > 3	-1.43, 1.85	0.068	-1.73, -0.32	0.005*	0.36 (0.18, 0.73)	0.005*
Treatment						
- No medication	Ref.		Ref.			
- Combined oral contraception	-1.43, -0.10	0.019	-1.37, -0.11	0.023*	0.48 (0.25, 0.90)	0.023*
- Progestin only oral contraception	-1.95, 0.16	0.022	-1.87, -0.15	0.023*	0.36 (0.15, 0.86)	0.023*
- Injectable contraception	-1.13, -0.20	0.001	-1.25, -0.43	< .001*	0.43 (0.29, 0.65)	0.001*
- Intrauterine device	-1.37, 0.80	0.604	-1.59, 0.61	0.385	0.61 (0.20, 1.84)	0.385
- Implantation	-1.65, 1.39	0.869	-1.48, 1.46	0.993	0.99 (0.23, 4.30)	0.993
Factor associated vitamin D level						
Smoking	-0.32, 1.05	0.297			1.44 (0.73, 2.86)	0.297
Sun exposure	-0.04, 1.05	0.161	-0.06, 0.22	0.236	1.66 (0.96, 2.86)	0.161
Cloth	-0.07, 0.71	0.107	-0.58, 0.71	0.094	1.38 (0.93, 2.03)	0.107
Sunscreen application	-0.18, 0.60	0.285			1.23 (0.83, 1.82)	0.285
Working	-0.69, 0.80	0.878			1.06 (0.50, 2.23)	0.878
Consuming fish						
- Less than 3 times/week	-0.95, 0.33	0.342			0.73 (0.39, 1.39)	0.342
- 3-5 times/week	-0.61, 0.78	0.807			1.09 (0.54, 2.18)	0.807
- Eating every day	-.136, 1.22	0.92			1.72 (0.87, 3.39)	0.920
Consuming egg						
- Less than 3 times/week	-0.70, 1.67	0.422			1.62 (0.50, 5.31)	0.422
- 3-5 times/week	-0.91, 1.47	0.642			1.32 (0.40, 4.35)	0.642
- Eating every day	-1.36, 1.22	0.691			0.93 (0.26, 3.39)	0.691
Drinking milk						
- Less than 3 times/week	-0.42, 0.57	0.761			1.08 (0.66, 1.77)	0.761
- 3-5 times/week	-0.60, 0.76	0.823			1.08 (0.55, 2.14)	0.823
- Eating every day	-0.33, 0.85	0.383			1.30 (0.72, 2.34)	0.383

Data were analyzed using univariate and multivariate logistic regression analysis, with a p value threshold of 0.2 in a univariate analysis and a p value threshold of 0.05 in the multivariate analysis.
Coeff: Coefficient, SE: standard error, SD: standard deviation
*significant level

Fig. 1 presents the correlation between the log total myoma volume and the log total vitamin D level. There was a significant inverse correlation between the log total myoma volume and the log vitamin D level among Thai women (Pearson correlation coefficient, r = -0.239; p = 0.023).

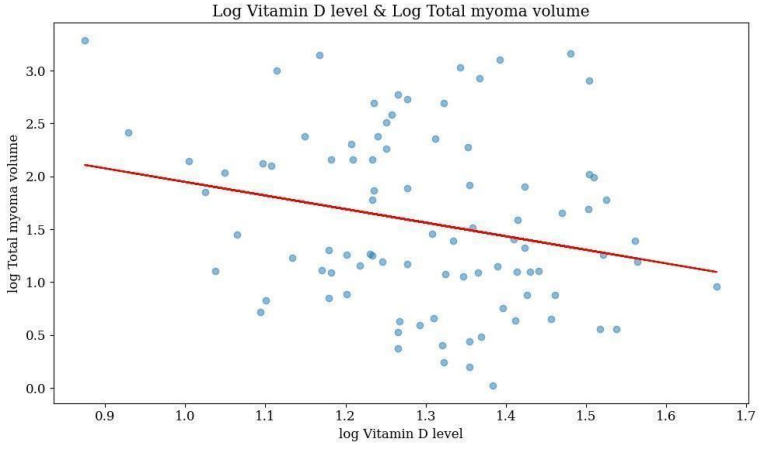

Fig. 1. Correlation between log total myoma volume and log vitamin D level.

Discussion

This study aimed to explore the relationship between uterine fibroid volume and vitamin D levels in Thai women, and we found that serum vitamin D levels were weakly and inversely correlated with uterine myoma volume among Thai women (Pearson correlation coefficient, r = -0.239; p = 0.023). This indicated that lower vitamin D levels were weakly associated with larger total myoma volumes. This finding was consistent with previous studies. For instance, a correlation study by Sarbhai (2021) in India, which reported a Pearson correlation coefficient of -0.292 between vitamin D levels and fibroid volume[10]. Similarly, Srivastava et al (2020)[14] found that lower vitamin D levels were associated with larger fibroid sizes, with a statistically significant difference (p = 0.014). In 2019, Singh also observes that as uterine fibroid volume increased, vitamin D levels significantly decreased (p < 0.044)[15].

The baseline characteristics, such as BMI, also showed a significant positive correlation with myoma volume. Interestingly, parity, particularly having more than 3 children, was associated with a reduced myoma volume.

Other factors associated with total uterine myoma volume included the use of combined oral contraceptives (coeff = -0.778, p = 0.019), progestin-only oral contraceptives (coeff = -1.051, p = 0.022), and injectable contraceptives (coeff = -0.702, p = 0.001). However, these findings differ from previous studies where combined oral contraceptives did not show any reduction in uterine myoma volume[16]. Earlier research has demonstrated a decrease in uterine myoma volume with progestin-only contraceptives, particularly dienogest[17].

Contrary to expectations, lifestyle factors such as sun exposure, sunscreen use, and diet did not significantly impact vitamin D levels in this cohort. This suggested that other factors, such as genetic predisposition or underlying health conditions, may play a more significant role in determining vitamin D levels in women with myoma uteri.

The prevalence of vitamin D deficiency among Thai women with uterine myomas was found to be 48.9%. Singh (2019) also identified vitamin D deficiency as a potential risk factor for myoma

development (p = 0.044), noting that larger myomas were associated with lower vitamin D levels[15]. A systematic review and meta-analysis that examined nine studies found that patients with uterine fibroids had significantly lower vitamin D levels than those without fibroids (p < 0.001). These findings highlighted the potential for exploring vitamin D supplementation as a non-invasive intervention to manage myoma growth.

The strengths of this study included its focus on Thai women, making the findings locally relevant. Additionally, by analyzing multiple factors (e.g., contraceptive use, sun exposure, and diet), the study offers a comprehensive view of influences on myoma volume, potentially guiding future treatment strategies.

However, the study had several limitations. Being a single center study, the result of this study may not represent all Thai women. Also, the accuracy of ultrasound measurements is operator-dependent, although our investigators measurements were standardized, it may still introduce minor errors in evaluating myoma volume. The small sample size may limit the statistical power to detect more subtle correlations. Finally, the lack of longitudinal follow-up prevents the study from assessing how changes in vitamin D levels or treatments may affect the growth or regression of myomas over time.

Lastly, the result of our study probably affirmed that vitamin D level was weak and inversely correlated to the fibroid volume. As uterine fibroids are very common and clearly hold negative impacts on women's quality of life, further study with more comprehensive designs and randomized-controlled trials about the use of vitamin D supplements as a choice of treatment for myoma volume reduction could be beneficial in this field of knowledge.

Conclusion

Serum vitamin D levels were weak and inversely correlated to the myoma uteri volume among Thai women. Further longitudinal and interventional research to determine whether vitamin D supplementation can be a viable strategy for managing fibroid growth are advocated.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Development and Internal Validation of Prediction Model on Delivery within 7 Days for Spontaneous Late Preterm Labor in Pregnancy: A retrospective cohort study

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ABSTRACT

Objectives: To develop and internally validate a predictive model for estimating the likelihood of delivery within 7 days of the onset of spontaneous late preterm labor.

Materials and Methods: We conducted a retrospective cohort study involving singleton pregnancies with late preterm labor (gestational age 34-36^{+6} weeks) from October 1, 2018, to September 30, 2023. Predictors were selected based on expert consensus and stepwise backward elimination. The model was developed using multivariable logistic regression, with performance assessed through calibration (slope and plot), discrimination area under the receiver operating characteristic curve (AUROC), and overall prediction (Brier score). Internal validation was performed using 10-fold cross-validation.

Results: The study included 371 pregnancies: 254 delivered within 7 days and 117 later. The optimal model, based on the selected performance metrics, was the multivariable logistic regression model. It demonstrated robust discrimination and overall predictive accuracy, with an AUROC of 0.860 (95% confidence interval (CI) 0.756-0.942) and a Brier score of 0.144 (95% CI 0.100- 0.206). Calibration metrics included a calibration-in-the-large of -0.002 (95% CI -0.076- 0.063) and a calibration slope of 6.102 (95% CI 2.596-12.208). Key predictors identified by the model were maternal age, gestational age at labor onset, coexisting infections, hypertension, cervical dilation, cervical effacement, uterine contractions, nulliparity, and coexisting diabetes.

Conclusion: The model accurately predicted delivery within 7 days of spontaneous late preterm labor, demonstrating high predictive performance in the studied cohort. This supports clinical decision-making and potentially optimizes the timely use of dexamethasone interventions.

Keywords: late preterm labor, prediction model, dexamethasone, pregnancy.

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การพัฒนาและการตรวจสอบภายในของแบบจำลองการทำนายการคลอดภายใน 7 วันสำหรับการเจ็บครรภ์คลอดก่อนกำหนดในระยะท้ายในหญิงตั้งครรภ์

รพีพัฒน์ นกหนู, ศรวัส แสงแก้ว, โคดีเย๊าะ กาเสาะ, สุนิษฐา สงวนเชื้อ

บทคัดย่อ

วัตถุประสงค์*: เพื่อพัฒนาและตรวจสอบภายในแบบจำลองการทำนายเพื่อประมาณความน่าจะเป็นของการคลอดภายใน 7 วันหลังจากเริ่มมีการเจ็บครรภ์คลอดก่อนกำหนดในระยะท้าย*

วัสดุและวิธีการ*: ทำการศึกษาแบบย้อนหลังในกลุ่มหญิงตั้งครรภ์เดี่ยวที่มีการเจ็บครรภ์คลอดก่อนกำหนดในระยะท้าย (อายุครรภ์ 34-36^{+6} สัปดาห์) ตั้งแต่วันที่ 1 ตุลาคม 2561 ถึง 30 กันยายน 2566 ตัวแปรทำนายการคลอดภายใน 7 วัน ถูกเลือกตามความเห็นของผู้วิจัยและการคัดเลือกถอยหลังแบบก้าวหน้า โมเดลถูกพัฒนาขึ้นโดยใช้การถดถอยโลจิสติกแบบพหุคูณ และประเมินการใช้โมเดลการทำนายาการคลอดโดยใช้ การปรับเทียบขนาดใหญ่และความลาดเอียงในการปรับเทียบ การแยกแยะโดยใช้พื้นที่ใต้กราฟ และการทำนายโดยรวม (Brier score) การตรวจสอบภายในดำเนินการโดยใช้ 10-fold cross-validation*

ผลการศึกษา*: การศึกษานี้รวบรวมหญิงตั้งครรภ์ 371 คน: 254 คนคลอดภายใน 7 วัน และ 117 คนคลอดหลังจาก 7 วัน โมเดลที่เหมาะสมที่สุดตามตัวชี้วัดประสิทธิภาพที่เลือกคือโมเดลการถดถอยลอจิสติกแบบพหุ ซึ่งแสดงให้เห็นถึงความสามารถในการจำแนกและความแม่นยำในการทำนายโดยรวมอย่างยอดเยี่ยม โดยมีค่าพื้นที่ใต้กราฟ 0.860 (95% confidence interval (CI) 0.756-0.942), และความสามารถโดยรวม Brier score 0.144 (95% CI 0.100-0.206) ความสามารถในการเทียบประกอบด้วยการปรับเทียบขนาดใหญ่ -0.002 (95% CI -0.076-0.063)และความลาดเอียงในการปรับเทียบ 6.102 (95% CI 2.596-12.208) ตัวแปรสำคัญที่มีผลต่อการทำนายการคลอด ได้แก่ อายุของมารดา, อายุครรภ์เมื่อเริ่มเจ็บครรภ์, การมีภาวะติดเชื้อร่วม, ความดันโลหิตสูง, การเปิดขยายของปากมดลูก, การบางตัวของปากมดลูก, จำนวนครั้งของการหดรัดตัวของมดลูก, การตั้งครรภ์แรก และภาวะเบาหวาน*

สรุป*: โมเดลนี้สามารถทำนายการคลอดภายใน 7 วันหลังการเจ็บครรภ์คลอดก่อนกำหนดในระยะท้ายได้อย่างแม่นยำ มีประสิทธิภาพในการทำนายสูงและช่วยในการตัดสินใจเลือกใช้ยาเดกซาเมทาโซน*

คำสำคัญ*: การตั้งครรภ์ก่อนกำหนดในระยะท้าย, แบบจำลองการทำนาย, เดกซาเมทาโซน, หญิงตั้งครรภ์*

Introduction

Preterm labor refers to the onset of labor between 20 and 36^{+6} weeks of gestation, accompanied by regular uterine contractions and cervical changes[1-2]. Infants born during this gestational period are at a higher risk of complications and mortality compared to those born at full term. Administering corticosteroids, such as dexamethasone, is the standard treatment to reduce the incidence of neonatal respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis in preterm infants[3-4]. In late preterm infants, corticosteroids have been shown to decrease the risk of severe respiratory complications, transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia. However, they do not significantly reduce the incidence of respiratory distress syndrome in late preterm newborns[5].

The practice guidelines of the Royal Thai College of Obstetricians recommend administering corticosteroids to women with preterm labor between 20 and 33^{+6} weeks of gestation. They also suggest considering corticosteroid administration for women in labor between 34 and 36^{+6} weeks who have not previously received this medication during the current pregnancy[1-3]. The optimal window for corticosteroid effectiveness is between 24 hours and 7 days after the first dose[6-8]. However, if the patient receives corticosteroids and delivers more than 7 days after administration, it may result in lower birth weight and increase the risk of psychological and neurocognitive problems in childhood[9-11].

Currently, factors that help predict delivery in patients diagnosed with preterm labor include history-taking, physical examination, cervical length measurement via ultrasound, and the detection of biomarkers[12-16]. Glover et al found that cervical dilation ≥ 4 cm is associated with a 60% sensitivity and 68% specificity for preterm delivery, while cervical effacement ≥ 75% has a sensitivity of 59% and specificity of 65%. Other significant factors include nulliparity and abnormal fetal presentation. Factors like age, body mass index, smoking, alcohol, drug use, infections, and uterine contractions were not significantly associated with preterm labor[13]. Wong et al found that cervical length ≤ 27.5 mm predicts delivery within 7 days with 77.8% accuracy at the initial measurement, and 100% accuracy 1 day after hospitalization[14]. Leow et al found that seven biomarkers, including interleukin-1 receptor antagonist, vitamin D binding protein, tissue inhibitor of metalloproteinases-1, pigment epithelium-derived factor, gamma-flutamyl hydrolase, laminin subunit famma 2, and extracellular matrix protein-1, can be used to predict the future occurrence of preterm labor with a sensitivity of 100% and a specificity of 78%[15]. Stock et al conducted research on a predictive model using vaginal fluid fetal fibronectin (fFN) to predict spontaneous preterm birth within 7 days. The study found that their model achieved an area under the curve (AUC) of 0.89[16]. However, Hat Yai Hospital lacks personnel and resources to accurately measure cervical length and does not have biomarker test kits to predict preterm delivery within 7 days. Therefore, this research aimed to create a model based on historical and physical examination data to identify preterm labor cases who likely to deliver within 7 days.

Materials and Methods

The prediction model for delivery within 7 days of preterm labor between 34-36^{+6} weeks of gestation was developed through a retrospective cohort study. The study spanned 5 years, from October 1, 2018, to September 30, 2023, at Hat Yai Hospital, Songkhla Province, Thailand. The study was approved by the Human Research Ethics Committee of Hat Yai Hospital (IRB: HYH-EC 082-66-01)

The participants were pregnant women with a singleton pregnancy who experienced preterm labor between 34^{+0} and 36^{+6} weeks of gestation. These women had regular uterine contractions, at least 4 in 20 minutes or 8 in 60 minutes, along with cervical dilation of 1 cm or more, and had already delivered at Hat Yai Hospital with a cephalic presentation.

Participants with preterm labor were excluded if they had conditions such as preterm premature rupture of membranes (PPROM), previous cesarean section, fetal growth restriction, or if they had received tocolysis

between 34^{+0} and 36^{+6} weeks. Other exclusion criteria included severe preeclampsia, hemolysis, elevated liver enzymes and low platelets syndrome, non-reassuring fetal status, active phase of labor with cervical dilation > 6 cm, suspected chorioamnionitis, oligohydramnios, intrauterine fetal demise, congenital fetal abnormalities, or cancer during pregnancy.

The sample size calculation for binary outcomes, using a 95% confidence interval, was based on statistics from Hat Yai Hospital. In one year, 69 women were diagnosed with preterm labor between 34^{+0} and 36^{+6} weeks, and 24 delivered within 7 days, approximately 30%. The calculated sample size was 322[17], with an additional 10% buffer to ensure completeness, making the total sample size 354. Data were entered using Epidata version 4.6.0.6. Patient characteristics and clinical information, including obstetric history, risk factors, and treatment outcomes, were analyzed using descriptive statistics. Categorical variables were reported as frequency and percentage. For continuous data, normally distributed variables were presented as mean ± standard deviation and compared using the independent t test. Non-normally distributed variables were summarized as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test (Ranksum test). For categorical data, the Fisher's exact test or chi square test was applied, depending on the expected frequencies in the contingency table. A p value < 0.05 was considered statistically significant.

Model development: candidate predictors were selected based on a literature review and statistical selection using stepwise backward elimination. The selected predictors were then used to build the model using logistic regression.

Internal validation: the accuracy of the model was evaluated using 10-fold cross-validation. Model performance was assessed using the Brier score for overall performance, calibration-in-the-large and calibration slope for calibration performance, and the C-index for discrimination performance[18]. Statistical analysis was performed using R version 4.4.1.

Results

A total of 1,071 women with spontaneous preterm labor were identified. Among them, 371 women met the inclusion criteria, while 700 were excluded (Fig. 1).

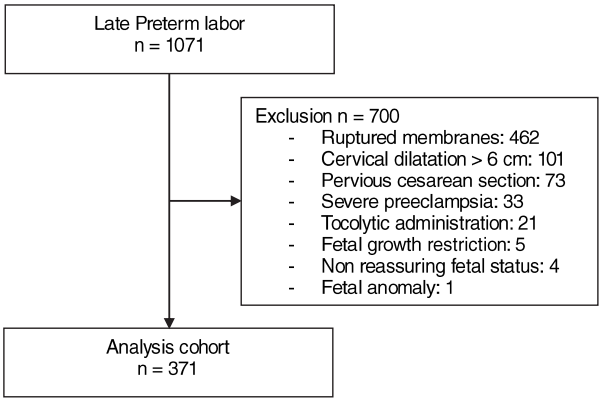

Fig. 1. A flow chart illustrating the exclusion process for conditions disrupting spontaneous labor or indicating termination before 37 weeks.

The participants were divided into two groups: those who delivered within 7 days of the onset of preterm labor (n = 254) and those who delivered more than 7 days after the onset (n = 117). Baseline and obstetric characteristics for both groups are presented in Table 1. The gestational age at the onset

of preterm labor was significantly higher in the group that delivered within 7 days compared to the group that delivered after 7 days (36.0 vs 35.4 weeks, p < 0.001). The group that delivered within 7 days had significantly greater cervical dilation (3 cm vs 2 cm, p < 0.001), thinner cervical effacement (80% vs 50%, p < 0.001), and a higher number of uterine contractions per hour (17 vs 14, p < 0.001). Additionally, this group was older (27 years vs 24 years, p = 0.025), had a higher prevalence of hypertension (13% vs 4.3%, p = 0.008), and greater substance use (7.1% vs 0.9%, p = 0.011).

Table 1. Demographic and pregnancy characteristics, and dexamethasone use of woman presenting with spontaneous late preterm labor, categorized by timing of delivery.

Demographic	Delivery within 7 days (n = 254)	Delivery after 7 days (n = 117)	Total (n = 371)	p value
Gestational age at trial entry (weeks) median (IQR)	36 (35.4, 36.6)	35.4 (34.7, 36.3)	36 (35.1, 36.4)	< 0.001
Maternal age (years) median (IQR	27 (22, 31)	24 (20, 29)	26 (21, 31)	0.025
Ethnic				
Thai (%)	239 (94.1)	112 (95.7)	351 (94.6)	0.518
Non-Thai (%) [a]	15 (5.9)	5 (4.3)	20 (5.4)	
BMI (kg/m^2) median (IQR)	25.4 (22.6, 28.2)	25.1 (22.8, 27.8)	25.4 (22.6, 28.1)	0.757
Nulliparity (%)	109 (42.9)	42 (35.9)	151 (40.7)	0.543
Interpregnancy interval (months) median (IQR)	15.5 (0, 60)	24 (0, 60)	20 (0, 60)	0.313
Previous spontaneous preterm birth (%)	25 (9.8)	14 (12)	39 (10.5)	0.536
Smoking (%)	24 (9.4)	10 (8.5)	34 (9.2)	0.78
Infection				
Urinary tract infection	10 (3.9)	11 (9.4)	21 (5.7)	0.055
Others [b]	3 (1.2)	3 (2.6)	6 (1.6)	
Substance use (%)	18 (7.1)	1 (0.9)	19 (5.1)	0.011
Underlying disease				
Hypertension (%)	34 (13.4)	5 (4.3)	39 (10.5)	0.008
Diabetes (%)	14 (5.5)	12(10.3)	26 (7)	0.096
Gestational diabetes managed with diet control (%)	4 (1.6)	7 (6)	11 (3)	0.023
Gestational diabetes managed with insulin (%)	5 (2)	5 (4.3)	10 (2.7)	
Pregestational diabetes (%)	5 (2)	0 (0)	5 (1.3)	
Hematocrit mean (SD), %	34.8 (3.5)	34.3 (3.7)	34.6 (3.6)	0.236
Cervical dilate (cm) median (IQR)	3 (2, 4)	2 (1, 2)	3 (2, 4)	< 0.001
Cervical effacement (%) median (IQR)	80 (60, 100)	50 (50, 70)	75 (50, 90)	< 0.001
Uterine contraction per hour median (IQR)	17 (14, 20)	14 (10, 19)	16 (12, 20)	< 0.001
Dexamethasone administration (%)				< 0.001
None	55 (21.6)	9 (7.7)	64 (17.2)	
Before 34 weeks	21 (8.3)	6 (5.1)	27 (7.3)	
After 34 weeks	178 (70.1)	102 (87.1)	280 (75.5)	
Onset of dexamethasone administration (%)				< 0.001
Within 24-hour	138 (69.4)	0 (0)	138 (45)	
Optimal time 24-hour-7 days	40 (20.1)	0 (0)	40 (13)	
Suboptimal time 7-14 days	5 (2.5)	32 (29.6)	37 (12)	
Ineffective > 14 days	16 (8)	76 (70.4)	92 (30)	

BMI: body mass index, IQR: interquartile range, SD: standard deviation

[a] includes Burmese or Cambodian, [b] includes acute gastroenteritis, COVID-19 infection, influenza infection.

The variables considered as independent predictors included maternal age, gestational age at the onset of labor, nulliparity, interpregnancy interval, hypertension, diabetes, hematocrit level, cervical dilation, cervical effacement, and the number of uterine contractions per hour.

The univariable analysis showed that women who delivered within 7 days (Table 2) were older (OR 1.04; 95% CI 1.00-1.07; p = 0.04), had a higher gestational age at the onset of labor (OR 1.82; 95% CI 1.40-2.37; p < 0.001), were fewer coexisting-infection (OR 0.4; 95% CI 0.18-0.87; p = 0.023), had a higher incidence of hypertension (OR 3.46; 95% CI 1.32-9.1; p = 0.004), had greater cervical dilation (OR 2.77; 95% CI 2.15-3.57; p < 0.001), had thinner cervical effacement (OR 1.06; 95% CI 1.05-1.08; p < 0.001), and experienced more uterine contractions (OR 1.07; 95% CI 1.03-1.12; p = 0.001).

Table 2. Univariable and multivariable logistic regression analysis of factors associated with delivery within 7 days in woman with spontaneous late preterm labor.

Factors	Univariate		Multivariate	
	OR (95%CI)	p value	OR (95%CI)	p value
Gestational age at trial entry	1.82 (1.4, 2.37)	< 0.001	1.42 (1.01, 1.98)	0.042
Maternal age	1.04 (1, 1.07)	0.04	1.11 (1.05, 1.18)	< 0.001
Nulliparous	1.34 (0.85, 2.11)	0.199	2.74 (1.36, 5.55)	0.004
Interpregnancy interval	0.9973 (0.9928, 1.0018)	0.245		
History of previous preterm	0.8 (0.4, 1.61)	0.54		
Infection	0.4 (0.18, 0.87)	0.023	0.39 (0.14, 1.06)	0.062
Hypertension	3.46 (1.32, 9.1)	0.004	3.97 (1.17, 13.49)	0.016
Diabetes [a]	0.51 (0.23, 1.14)	0.106	0.18 (0.06, 0.57)	0.003
Hematocrit	1.04 (0.98, 1.1)	0.236		
Cervical dilate	2.77 (2.15, 3.57)	< 0.001	1.95 (1.41, 2.69)	< 0.001
Cervical effacement	1.06 (1.05, 1.08)	< 0.001	1.04 (1.02, 1.06)	< 0.001
Uterine contraction	1.07 (1.03, 1.12)	0.001	1.07 (1.01, 1.12)	0.012

[a] includes pregestational diabetes, gestational diabetes managed with diet and exercise, and gestational diabetes managed with insulin.
OR: odds ratio, CI: confidence interval

When the variables were selected using multivariable logistic regression through stepwise backward elimination, main predictors (Table 2) included maternal age (aOR 1.11; 95% CI 1.05-1.18), gestational age at labor onset (aOR 1.42; 95% CI 1.01-1.98), coexisting infections (aOR 0.39; 95% CI 0.14-1.06), hypertension (aOR 3.97; 95% CI 1.17-13.49), cervical dilation (aOR 1.95; 95% CI 1.41-2.69), cervical effacement (aOR 1.04; 95% CI 1.02-1.06), uterine contractions (aOR 1.07; 95% CI 1.01-1.12), nulliparity (aOR 2.74; 95% CI 1.36-5.55), and coexisting diabetes (aOR 0.18; 95% CI 0.06-0.57).

The final model, as detailed in Fig. 2, effectively predicted the likelihood of late preterm delivery within 7 days. This was demonstrated by its strong discriminatory power, with a C-index of 0.860 (95% CI 0.756-0.942). A C-index value closer to 1 indicates a highly discriminative model, meaning the model has a high ability to distinguish between those who deliver within 7 days and those who do not. The C-index value of 0.860 is considered excellent and supports the model's reliability for risk prediction.

The final model can be used to calculate the probability of delivery within 7 days using the following logistic regression model:

Where X= -19.88673 + (0.34793 * gestational age at trial entry in weeks) + (0.10856 * maternal age in years) + (1.00928 * nulliparous) – (0.95089*coexisting infection) + (1.38002*hypertension) + (0.66747* cervical dilation in centimeters) + (0.03810 * cervical effacement in percent) + (0.06433 * number of uterine contractions per hour) – (1.700648 * diabetes)

All variables are coded as binary (1 when present and 0 when absent) except for Gestational age at trial entry, maternal age, cervical dilatation, cervical effacement and number of uterine contractions per hour which are continuous

Once X is calculated, it can be transformed into the probability of delivery within 7 days using the formula:

$$P(X) = \frac{1}{1 + e^{-X}}$$

Fig. 2. Full prediction model to allow individualized predictions for delivery within 7 days in woman with spontaneous late preterm labor.

The model's calibration was evaluated using a calibration plot (Fig. 3), which showed strong agreement between predicted risks and actual outcomes, indicating its accuracy in predicting preterm delivery. The calibration-in-the-large was -0.002 (95% CI -0.076-0.063), suggesting that the model's predictions were unbiased, with no significant overestimation or underestimation of risk. The calibration slope, which measures how well predictions align with observed outcomes across different risk levels, was 6.102 (95% CI 2.596-12.208). A value closer to 1 would indicate perfect calibration, while the values above 1 suggest more extreme predictions than actual outcomes. In this case, the slope indicates that the model slightly overestimates risk, but this is still within an acceptable range for model performance.

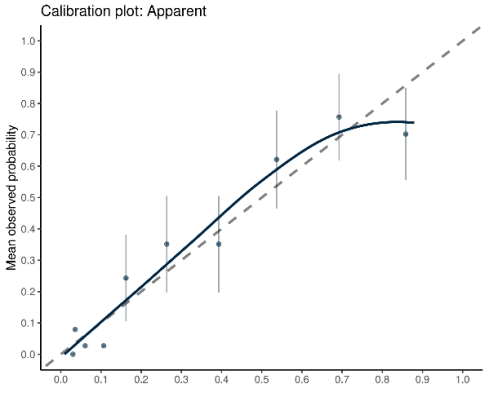

Fig. 3. This calibration plot compares the predicted probabilities from the model with the observed probabilities. The dashed diagonal line represents perfect calibration, where predicted probabilities perfectly match observed probabilities. The solid line represents the smoothed calibration curve for the model, indicating the relationship between predicted and observed probabilities. Error bars represent 95% confidence intervals for the observed probabilities in each decile of predicted risk.

Finally, the overall performance of the model was quantified using the Brier score, which evaluates the accuracy of probabilistic predictions by measuring the mean squared error between predicted and observed probabilities. The Brier score for the model was 0.144 (95% CI 0.100-0.206), with lower values indicating better model performance. The score suggests that the model provides reasonably accurate risk predictions, as lower Brier scores are desirable in risk prediction models.

The pregnant women were categorized into five groups based on their receipt of corticosteroids as follows: 1) the group that did not receive corticosteroids (64 out of 371, 17.3%), 2) the group that delivered within 24 hours after receiving the first corticosteroid dose (138 out of 371, 37.2%), 3) the group that delivered at the optimal time, between 24 hours and 7 days after the first dose (40 out of 371, 10.8%), 4) the suboptimal group, which delivered between 7 and 14 days after the first dose (37 out of 371, 10%), and 5) the ineffective group, which delivered more than 14 days after the first dose (92 out of 371, 24.7%).

The study presented neonatal outcomes (Table 3). The median gestational age at birth, ranked from highest to lowest, was as follows: the ineffective group, the optimal group, the group that did not receive corticosteroids, the suboptimal group, and the group that delivered within 24 hours, with gestational ages of 38.2, 37.4, 36.7, 36.1, and 36.1 weeks, respectively ($p < 0.001$).

Table 3. Neonatal characteristics and outcomes stratified by time of delivery after dexamethasone administration.

Dexamethasone administration	No (n = 64)	Within 24 hours (n = 138)	Optimal time (n = 40)	Suboptimal time (n = 37)	Ineffective (n = 92)	p value
Birth weight median (IQR)	2732.5 (2581.2, 2955)	2585 (2290, 2840)	2537.5 (2313.8, 2692.5)	2840 (2520, 3015)	2977.5 (2721.2, 3193.8)	< 0.001
Gestational age of delivery median (IQR)	36.7 (36.2, 37)	36.1 (35.6, 36.6)	36.1 (35.6, 36.5)	37.4 (36, 38.1)	38.2 (37.4, 39.1)	< 0.001
Administration to care unit (%)	20 (31.2)	50 (36.2)	14 (35)	8 (21.6)	16 (17.4)	0.023
Length of stay median (IQR)	3.7 (2.7, 5.6)	3.6 (2.7, 6.5)	3.6 (2.7, 5.6)	3.6 (2.7, 4.6)	3.6 (2.7, 4.6)	0.158
Respiratory event a	12 (18.8)	27 (19.6)	7 (17.5)	3 (8.1)	7 (7.6)	0.077
Transient tachypnea of the newborn (%)	11 (17.2)	22 (15.9)	6 (15)	3 (8.1)	7 (7.6)	0.262
Meconium aspiration syndrome (%)	1 (1.6)	0 (0)	1 (2.5)	0 (0)	0 (0)	0.144
Respiratory distress syndrome (%)	0 (0)	4 (2.9)	0 (0)	0 (0)	0 (0)	0.313
Persistent Pulmonary Hypertension of theNewborn (%)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	1
Mechanical (%)	1 (1.6)	7 (5.1)	0 (0)	0 (0)	1 (1.1)	0.292
Early onset sepsis (%)	12 (18.8)	27 (19.6)	5 (12.5)	3 (8.1)	9 (9.8)	0.167
Hypoglycemia (%)	8 (12.5)	27 (19.6)	4 (10)	2 (5.4)	3 (3.3)	0.003
Necrotizing enterocolitis (%)	2 (3.1)	3 (2.2)	1 (2.5)	0 (0)	0 (0)	0.385
Hyperbilirubinemia (%)	33 (51.6)	75 (54.3)	21 (52.5)	13 (35.1)	34 (37)	0.044

[a] include respiratory distress syndrome, persistent pulmonary hypertension of the newborn, transient tachypnea of the newborn.
IQR: interquartile range

Respiratory distress events after birth, including meconium aspiration syndrome, respiratory distress syndrome, transient tachypnea of the newborn, and persistent pulmonary hypertension, were most commonly observed in the group that delivered within 24 hours (19.6%). In this group, 7 cases (5.1%) required intubation. Additionally, intubation was required in 1 case (1.6%) in the group that did not receive corticosteroids and in 1 case (1.1%) in the ineffective group.

Other complications frequently observed in the group that delivered within 24 hours included early-onset sepsis (19.6%), hypoglycemia (19.6%), and hyperbilirubinemia (54.3%). One stillbirth, attributed to placental abruption, occurred in the group that delivered more than 14 days after spontaneous preterm labor.

Discussion

In developing a model based on clinical characteristics and laboratory findings to predict delivery within 7 days, nine predictors were identified as relevant: maternal age, gestational age at labor onset, coexisting infections, hypertension, cervical dilation, cervical effacement, uterine contractions, nulliparity, and diabetes. These predictors were consistent with previous research[15]. The results of the final model presented in this study highlight its strong performance in predicting the likelihood of late preterm delivery within 7 days. This model demonstrated excellent discriminatory power, as evidenced by a high C-index of 0.860 (95% CI 0.756–0.942). A C-index above 0.80 is generally considered excellent, indicating that the model can effectively identify individuals at higher or lower risk, thereby helping healthcare providers to make timely interventions.

Current research on predicting delivery within 7 days has highlighted similar factors. The study by Glover et al in 2019[13] found that cervical dilation of ≥ 4 cm and cervical effacement of ≥ 75% yielded a sensitivity of 82%, specificity of 75%, and an AUC of 0.69. In contrast, our study achieved a higher AUC, suggesting enhanced predictive ability. The difference in cervical dilation values was due to our enrollment of participants with smaller cervical dilation. Nonetheless, nulliparity aligned with these findings, as physiological dilation and/or effacement are more common in multiparous women. Previous studies have utilized transvaginal ultrasound[14] to calculate preterm birth within one week, showing that a cervical length cut-off of 27.5 mm could predict delivery within one week with 77.8% accuracy. Incorporating cervical length measurement via transvaginal ultrasound or testing for biochemical markers, such as fetal fibronectin, could further enhance the model's performance.

The calibration performance, assessed through the calibration plot, showed good alignment between predicted risks and observed outcomes, confirming the model's accuracy. The calibration-in-the-large value of -0.002 (95% CI -0.076-0.063) indicated no significant overestimation or underestimation of risk, ensuring the model's reliability. The calibration slope of 6.102 (95% CI 2.596-12.208) suggested that the model tended to overestimate risks, particularly for higher-risk individuals. While this may lead to unnecessary interventions in some cases, early identification of high-risk individuals in preterm labor can help mitigate adverse outcomes, making this slight overprediction beneficial.

The Brier score of 0.144 (95% CI 0.100–0.206) further supports the model's accuracy in predicting the risk of late preterm delivery. A lower Brier score indicates better model performance, and the value observed in this study suggests that the model provides accurate and reliable risk predictions. The Brier score complements the C-index and calibration measures, offering a holistic view of the model's effectiveness. Future development could include creating a program that calculates the score by simply entering parameter values.

However, this was a retrospective study in which the data obtained relied on medical records. The measurement of cervical dilation and effacement was based on physical examinations, which are subject to variation. Additionally, the participants included both early and late antenatal care attendees, leading to differences in the accuracy of gestational age for each individual. Therefore, external validation of this model through a multicenter prospective study is recommended. Furthermore, integrating cervical length assessments may enhance the clarity and accuracy of the predictions.

According to the WHO (2015), research from the Cochrane Database indicates that the optimal time

for corticosteroid administration to benefit newborns is between 24 hours and 7 days[6]. A study by Hackney et al in 2013 found that most deliveries did not occur within 7 days after corticosteroid administration[7]. Additionally, research by Humbeck et al revealed that only 20.8% of deliveries occurred within the optimal time window of 24 hours to 7 days. In the present study conducted at Hat Yai Hospital, only 13% of women received corticosteroids and delivered within this optimal time window[8]. The lower rate observed in this research may be attributed to the exclusion of women with conditions such as preeclampsia, premature rupture of membranes, and fetal growth restriction, all of which are associated with a higher likelihood of delivering within the optimal corticosteroid window.

In this study, corticosteroid administration for women with spontaneous preterm labor was categorized into five groups based on the timing of the treatment. These groups exhibited varying gestational ages at delivery. Notably, the longer the interval between the onset of preterm labor and corticosteroid administration, the greater the gestational age at birth, which in turn contributed to a reduction in neonatal complications as gestational age increased.

When comparing the groups that did not receive corticosteroids, the group that delivered within 24 hours, and the group that delivered within the optimal time frame, all three groups had similar gestational ages at birth, all falling within the late preterm period. They also exhibited comparable complications, including respiratory distress, early-onset sepsis, neonatal hypoglycemia, necrotizing enterocolitis, and jaundice. A study by Gyamfi-Bannerman et al (2016) demonstrated that corticosteroid administration could reduce severe respiratory complications[5]. However, in this study, the number of severe respiratory complications was limited, which restricted the ability to assess the benefits of corticosteroid use. Additionally, the study faced limitations related to sample size, which was insufficient to differentiate between low-incidence events.

Conclusion

In conclusion, the final model presented in this study demonstrated strong discriminatory power, excellent calibration, and overall good performance in predicting late preterm delivery within 7 days. Its robust performance metrics suggested that it could be a useful tool for clinical decision-making in optimally used dexamethasone managing late preterm labor. However, further external validation and consideration of other potential risk factors will be necessary to confirm its applicability across different populations and clinical settings.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Effect of Face Mask Wearing on Maternal Oxygen Saturation and on Non-stress Test Results

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ABSTRACT

Objectives: This study was conducted to evaluate the maternal oxygen saturation at the 5th minute, as measured by pulse oximetry and non-stress test (NST) results in pregnant women when they were not wearing and wearing a face mask.

Materials and Methods: A prospective observational study was conducted among pregnant women with a gestational age ≥ 32 weeks. Each participant was monitored for maternal oxygen saturation, as measured by pulse oximetry, vital signs, and NST for approximately 40 minutes divided into 20-minute durations under conditions of them not wearing and wearing a face mass, respectively.

Results: In total, 72 participants were enrolled. The mean maternal oxygen saturation was significantly lower at the 5th minute of monitoring the pregnant women when wearing a face mask than at the 5th minute when not wearing a face mask (mean ± standard deviation (SD) = 97.78 ± 1.24% vs 98.15 ± 1.12%, p = 0.009). The mean maternal diastolic blood pressure was also significantly lower at the 5th minute of monitoring participants when wearing a face mask versus not wearing a face mask (mean ± SD = 66.32 ± 7.60 mmHg vs 68.40 ± 8.13 mmHg, p = 0.007). Non-reactive NST results are comparable when wearing and not wearing a face mask (p = 0.313).

Conclusion: The mean maternal oxygen saturation and maternal diastolic blood pressure were significantly lower at the 5th minute of monitoring the participants when wearing a face mask than at the 5th minute when not wearing a face mask, but the trend was no difference when monitoring for a longer time.

Keywords: oxygen saturation, non-stress test, pregnancy, face mask.

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ผลของการใส่หน้ากากอนามัยต่อระดับออกซิเจนปลายนิ้วมือและการตรวจสุขภาพทารกในหญิงตั้งครรภ์ช่วงท้ายไตรมาสสาม

ภัทราพร อุดมพรธนกิจ, กิตติพงษ์ คงสมบูรณ์, ธารารัตน์ หาญประเสริฐพงษ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาระดับออกซิเจนปลายนิ้วโดยการวัดความอิ่มตัวออกซิเจนของฮีโมโกลบินจากซีพจร ณ. นาทีที่ 5 และตรวจสุขภาพทารกของหญิงตั้งครรภ์ ขณะก่อนและหลังใส่หน้ากากอนามัย*

วัสดุและวิธีการ: *เป็นการศึกษาแบบไปข้างหน้าโดยเก็บข้อมูลจากหญิงตั้งครรภ์เดี่ยวจำนวน 72 ราย ที่มีอายุครรภ์มากกว่า 32 สัปดาห์ขึ้นไป โดยหญิงตั้งครรภ์จะได้รับการตรวจระดับออกซิเจนปลายนิ้วโดยการวัดความอิ่มตัวออกซิเจนของฮีโมโกลบินจาก ซีพจร และทดสอบสุขภาพทารกของหญิงตั้งครรภ์ด้วยวิธี non stress test เป็นเวลา 40 นาที โดยแบ่ง เป็นช่วงที่ไม่ใส่หน้ากากอนามัยและใส่หน้ากากอนามัยช่วงละ 20 นาที ตามลำดับ*

ผลการศึกษา: *จากจำนวนหญิงตั้งครรภ์ทั้งหมด 72 ราย พบว่าค่าเฉลี่ยระดับออกซิเจนปลายนิ้วที่เวลา 5 นาที หลังจากใส่หน้ากากอนามัยมีค่าต่ำกว่าอย่างมีนัยสำคัญทางสถิติ เมื่อเปรียบเทียบกับที่เวลา 5 นาที หลังจากถอดหน้ากากอนามัย โดยมีค่าเฉลี่ยของระดับออกซิเจนปลายนิ้ว (ค่าเฉลี่ย ± ค่า เบี่ยงเบนมาตรฐาน = ร้อยละ 97.78 ±1.24 และ ร้อยละ 98.15 ±1.12, ค่าความน่าจะเป็น = 0.009) และพบว่าค่าเฉลี่ยระดับความดันโลหิตขณะหัวใจคลายตัวที่เวลา 5 นาที หลังจากใส่หน้ากากอนามัย มีค่าต่ำกว่าอย่างมีนัยสำคัญ เมื่อเปรียบเทียบที่เวลา 5 นาที หลังจากถอดหน้ากากอนามัยเช่นกัน (ค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐาน = 66.32 ± 7.6 มิลลิเมตรปรอท และ 68.40 ± 8.13 มิลลิเมตรปรอท, ค่าความน่าจะเป็น = 0.007) ความผิดปกติของสุขภาพทารกในครรภ์ (Non-reactive NST) พบได้ไม่แตกต่างกันในขณะใส่และไม่ใส่หน้ากากอนามัย (ค่าความน่าจะเป็น = 0.313)*

สรุป: *ค่าเฉลี่ยระดับออกซิเจนปลายนิ้วและระดับความดันโลหิตขณะหัวใจคลายตัวที่เวลา 5 นาที หลังจากใส่หน้ากากอนามัยมีค่าต่ำกว่าอย่างมีนัยสำคัญ เมื่อเปรียบเทียบที่เวลา 5 นาที หลังจากไม่ใส่หน้ากากอนามัย แต่ค่ามีแนวโน้มไม่แตกต่างกัน เมื่อติดตามในระยะเวลาที่นานขึ้น*

คำสำคัญ: *ระดับออกซิเจนปลายนิ้ว, การตรวจสุขภาพทารกในครรภ์, การตั้งครรภ์, หน้ากากอนามัย*

Introduction

The coronavirus infection (COVID-19) was first reported in Wuhan, China, in December 2019, and was ultimately found to be caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain of coronavirus; the common symptoms of which are fever, fatigue, dry cough, myalgia, and headache. Moreover, in severe cases, the affected patient may present with hemoptysis, dyspnea, and pneumonia[1, 2]. The World Health Organization (WHO) estimated the virus has an overall mortality rate of around 3% - 4%[3, 4]. Some pregnant with COVID-19 had serious morbidity and required intensive care unit admission, and preterm delivery occurred in around 47% of the pregnant women hospitalized with COVID-19[5]. Further, the fetal effects of COVID-19 were noted that the risk of important adverse prenatal and perinatal adverse outcomes, including miscarriage, premature rupture of the membranes, and fetal growth restriction, were increased[6]. Moreover, medical prescription for pregnant women is highly difficult and complicated. Thus, protecting pregnant women from COVID-19 should be a key issue. In this regard, three effective safety methods are universally promoted. The first is the wearing of a face mask, especially when other social distancing measures are difficult to practice and when it is not easy to avoid other people who are not wearing masks; the second is to ensure social distancing by staying at least 6 feet away from other people outside your household; and the last is washing the hands with soap and water for at least 20 seconds or with a hand sanitizer with at least a 60% alcohol content if soap and water are not available[7]. The face mask should be made with at least two layers of fabric or thick densely woven cotton[8]. Until now, the effect of face mask wearing on maternal oxygenation and on the fetus has not previously been evaluated. Consequently, this study was conducted to evaluate the maternal oxygen saturation at the 5th minute, as measured by pulse oximetry, in healthy pregnant women with a gestational age of more than 32 weeks of gestation under conditions of not wearing and wearing a face mask. The secondary aim of this study was also to evaluate the maternal oxygen saturation at the 15th and 20th minute and to identify the effect of face mask wearing on the non-stress test (NST) results. Last, the tertiary aim was to assess the level of discomfort feeling in the pregnant women without and with face mask wearing.

Materials and Methods

This prospective observational study was conducted among singleton healthy pregnant women with a gestational age of more than 32 weeks of gestation who attended the Antenatal Outpatient Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Thailand, between December 2020 and March 2021. Exclusion criteria were women who had labor pain, abnormal vaginal bleeding, rupture of the membranes, fever, hypertension, chronic lung or respiratory tract disorder, including asthma, pneumonia, cardiovascular, or circulatory disorder, past or current smoking, overt diabetes mellitus, fetal growth or structural abnormalities, abnormal amount of amniotic fluid, and those who refused to participate. The study was approved by the institute ethics committee (Srinakharinwirot University Ethics committee-386/2563F) and was registered with the Thai Clinical Trials Registry (TCTR20201124002: 24/11/2020).

After the routine antenatal care (ANC) was completed, we explained the details of our study to the pregnant women. The pregnant women who agreed to participate in our study were asked to complete an informed consent form. Informed consent was obtained from all study participants. The participants were asked to complete their demographic information, including maternal age, race, parity, most reliable gestational age, height, weight, body mass index (BMI), and any underlying disease. All the participants were evaluated for fetal presentation,

estimated fetal weight, and amniotic fluid index by ultrasonographic examination (US). Average US was taken approximately 15 minutes where every participant will be rest and limit their activity in the same. Then, each participant was monitored for maternal oxygen saturation, as measured by pulse oximetry, maternal vital signs, and NST for approximately 40 minutes divided into 20-minute durations under conditions of them not wearing and wearing a face mask, respectively. GE Carescape V100, USA device was used for continuously measured the maternal vital signs and pulse oximetry to all participants. Fetal heart rate (FHR) baseline, baseline FHR variability and number of FHR acceleration/deceleration were the NST components of interest. Reactive NST defined as two or more accelerations peaking at 15 beats per minute (bpm) or more above baseline, each lasting 15 seconds or more, and all occurring within 20 minutes of them not wearing and wearing a face mask. If less than two accelerations found lasting to 30 minutes of them wearing and not wearing a face mask, the non-reactive NST was interpreted. NST was interpreted by the Maternal Fetal Medicine doctor who had received the maternal fetal medicine diploma from the Royal Thai College of Obstetricians and Gynaecologists and blinded for timing and participants' face mask wearing status. If the disconcordant interpretation occurred, both of them will discuss and finally conclude together.

The maternal oxygen saturation level and other vital sign variables were recorded at the 5th, 15th, and 20th minutes without and with face mask wearing. Proper face mask wearing was ensured by advising on the importance for the mask to cover the nose and mouth and also for it be secured under the chin. The face masks in our study were three-layer, ear-loop, disposable, melt-blown polypropylene surgical masks (Topwholesome company). The surgical face mask in our study was qualified the production by Thai food and drug administration and international organization for standardization. During the monitoring, all the participants used the same brand face masked and were positioned in the left lateral decubitus position in a separate room. All the study researchers wore a face mask all the time when inside the room. Participants were asked to demonstrate any discomfort feeling they experienced using visual analogue scales (VAS) at the 5th, 15th, and 20th minutes when not wearing and wearing the face mask. The VAS is measurement methods applied to measure a discomfort feeling level that is subjective and difficult to measure directly. The participants were asked to indicated a point along a 10 cm horizontal line (0 = no discomfort feeling and 10 = worst possible discomfort feeling)[9].

The required sample size was estimated using the two-dependent means for paired or matched samples study formula as per the dependent t-test. From a pilot study, we found that the mean oxygen saturations measured by pulse oximetry at the 5th minute in pregnant women with a gestational age of more than 32 weeks of gestation without and with face mask wearing were 97.9% and 97.4%, respectively. The standard deviation for the oxygen saturation measured by pulse oximetry in pregnant women with a gestational age of more than 32 weeks of gestation without face mask wearing was 1.35. To achieve an alpha of 0.05, beta of 0.2, and allowing for 20% lost or missing data, it was determined that at least 70 participants were required.

The demographic and clinical characteristics of the participants at baseline were presented as numbers and percentages or means and the standard deviation. The oxygen saturation measured by pulse oximetry, heart rate, blood pressure, body temperature, and respiratory rate of the participants without and with face mask wearing were compared using the dependent t-test at the 5th, 15th, and 20th minutes. Each variable component of the NST of the participants without and with face mask wearing was compared using the Wilcoxon signed-rank test and chi-square test. Lastly, the VAS level of the participants' discomfort feeling at the 5th, 15th, and 20th minutes without and with face mask wearing were compared at set times using the Wilcoxon signed-rank

test. In all the statistical tests, p values of < 0.05 were considered significant. The statistical analysis was performed with R2.10.0 software (freeware distributed by the R Development Care Team).

Results

In total, 72 pregnant women were enrolled on the study. The demographic and clinical data of the participants are presented in Table 1.

Table 1. Demographic characteristics of the enrolled patients (n = 72).

Clinical variables	
Age (years), mean ± SD	27.6 ± 6.02
Race, n (%)	
Thai	51 (70.8 %)
Others	21 (29.2 %)
Nulliparous, n (%)	
Yes	27 (37.5 %)
No	45 (62.5 %)
Delivery route of previous pregnancy, n (%)	
Vaginal delivery	38 (52.8%)
Cesarean section	7 (9.7%)
Gestational age (days), mean ± SD	146.9 ± 8.63
Gestational age (weeks), n (%)	
$32–33^{+6}$ weeks	10 (13.9 %)
$34–36^{+6}$ weeks	28 (38.9 %)
≥ 37 weeks	34 (47.2 %)
Height (cm), n (%)	
≤ 145	1 (1.4 %)
> 145	71 (98.6 %)
BMI (kg/m^2), n (%)	
Underweight (< 18.5)	0 (0 %)
Normal weight (18.5–24.9)	27 (37.5 %)
Overweight (25–29.9)	31 (43.1 %)
Obese (> 29.9)	14 (19.4 %)

SD: standard deviation, BMI: body mass index

Table 2 presents a comparison of the participants maternal oxygen saturation, heart rate, systolic and diastolic blood pressure, body temperature, and respiratory rate at the 5^{th}, 15^{th}, and 20^{th} minutes without and with face mask wearing. The mean maternal oxygen saturation was significantly lower at the 5^{th} minute with face mask wearing than at the 5^{th} minute without face mask wearing (mean ± SD = 97.78 ± 1.24% vs 98.15 ± 1.12%, p = 0.009). The mean maternal diastolic blood pressure was significantly lower at the 5^{th} minute with face mask wearing than at the 5^{th} minute without face mask wearing (mean ± SD = 66.32 ± 7.60 mmHg vs 68.40 ± 8.13 mmHg, p = 0.007).

Table 2. Comparison of the oxygen saturation, heart rate, blood pressures, and body temperature of participants without and with face mask wearing.

Variables	Without face mask wearing (mean ± SD)	With face mask wearing (mean ± SD)	Mean difference (95%CI)	p value*
Oxygen saturation (%)				
at 5th minute	98.15 ±1.12	97.78 ± 1.24	0.42 (0.11–0.73)	0.009
at 15th minute	97.79 ± 1.06	97.79 ± 1.16	0.03 (0.29–0.23)	0.83
at 20th minute	97.78 ± 1.24	97.89 ± 1.15	0.11 (0.37–0.15)	0.40
Heart rate (bpm)				
at 5th minute	87.9 ± 13.54	87.8 ± 12.61	0.056 (2.5–2.6)	0.966
at 15th minute	89.9 ± 17.6	88.8 ± 11.12	1.139 (2.6–4.89)	0.547
at 20th minute	89.2 ± 12.12	88.58 ± 12.83	0.639 (1.162–2.44)	0.482
Systolic blood pressure (mmHg)				
at 5th minute	110.81 ± 9.59	109.04 ± 13.71	1.764 (1.511–5.039)	0.287
at 20th minute	109.14 ± 8.51	108.97 ± 8.75	0.167 (1.586–1.919)	0.850
Diastolic blood pressure(mmHg)				
at 5th minute	68.4 ± 8.13	66.32 ± 7.60	2.056 (0.578–3.533)	0.007
at 20th minute	66.85 ± 7.35	66.92 ± 7.65	0.069 (1.532–1.393)	0.925
Body temperature (degree Celsius)				
at 5th minute	36.45 ± 0.45	36.48 ± 0.49	0.038 (0.1788–0.101)	0.581
at 20th minute	36.48 ± 0.47	36.48 ± 0.48	0.001 (0.131–0.128)	0.983
Respiratory rate (breaths per minute)				
at 5th minute	18.89 ± 1.49	19.06 ± 1.57	0.167 (0.47–0.136)	0.276
at 20th minute	18.83 ± 1.49	18.92 ± 1.46	0.083 (0.338–0.172)	0.516

* Dependent t-test.

bpm: beats per minute, SD: standard deviation, CI: confidence interval

Table 3 and 4 present comparisons of each variable component of the NST results of the participants without and with face mask wearing and information on the non-reactive NST cases, respectively. All the NST records were of a good quality for interpretation. Non-reactive NST results were comparable when wearing and not wearing a face mask (p = 0.313). Overall, 5/13 participants showed non-reactive NST in both cases, with and without face mask wearing, but only 1 case revealed an adverse pregnancy outcome, which involved thick meconium-stained amniotic fluid and needed emergency cesarean delivery. For the remaining 4 non-reactive NST cases, the additional biophysical profile variables, including fetal breathing, fetal tone, fetal movement, and amount of amniotic fluid, were normal. Then, repeat NST was performed on the same day and the results revealed reactive NST. Thus, the pregnancies were continued and all the cases ultimately delivered healthy newborns without

any adverse pregnancy outcome. For all the reactive NST cases in participants with and without face mask wearing, no adverse neonatal pregnancy was presented within 1 week of the test. The true positive rate value of NST in our study was 20% (1 adverse neonatal outcome case out of 5 non-reactive NST cases in participants with and without face mask wearing). The true negative rate value of NST in our study was 94% (67 reactive NST cases during tests in participants with or without face mask wearing out of 71 cases of no adverse pregnancy outcome within 1 week of the test).

Table 3. Comparison of each variable component of non-stress test of participants without and with face mask wearing.

Variables	Without face mask wearing	With face mask wearing	p value
FHR baseline (bpm) median (IQR)			
at 5th minute	140 (130-145)	140 (130-145)	0.908*
at 20th minute	140 (130-145)	140 (130-145)	0.752
Baseline variability			
at 5th minute			0.084**
Minimal	20 (27.8)	15 (20.8)	
Moderate	48 (66.7)	54 (75)	
Mark	4 (5.6)	3 (4.2)	
at 20th minute			0.064**
Minimal	19 (26.4)	13 (18.1)	
Moderate	49 (68.1)	54 (75)	
Mark	4 (5.6)	5 (6.9)	
Number of accelerations during 20 minutes median (IQR)	5 (3-8)	6 (4-9)	0.261*
Number of decelerations at 10 minutes			1.000**
No	68 (94.4)	69 (95.8)	
Early deceleration	0	0	
Late deceleration	0	0	
Variable deceleration	4 (5.6)	3 (4.2)	
At 20 minutes			1.000**
No	70 (97.2)	71 (98.6)	
Early deceleration	0	0	
Late deceleration	0	0	
Variable deceleration	2 (2.8)	1 (1.4)	
NST interpretation, n(%)			0.313**
Reactive	61 (84.7)	65 (90.3)	
Non-reactive	11 (15.3)	7 (9.7)	

* Wilcoxon signed-rank test, **chi-square test.

FHR: fetal heart rate, bpm: beats per minute, IQR: interquartile range, NST: non-stress test

Table 4. Information of non-reactive non-stress test cases in this study.

Case	Without face mask wearing	With face mask wearing	Information and result of pregnancy
1	Non-reactive	Reactive	$G_4P_2A_1$ 37^{+5} weeks, continued pregnancy until normal vaginal delivery at 38^{+4} weeks, healthy 3,610 g newborn, no abnormality
2	Reactive	Non-reactive	$G_4P_2A_1$ 35^{+5} weeks, continued pregnancy until normal vaginal delivery at 38^{+2} weeks, healthy 3,120 g newborn, no abnormality
3	Non-reactive	Reactive	$G_2P_0A_1$ 36^{+5} weeks, continued pregnancy until normal vaginal delivery at 37^{+2} weeks, healthy 2,360 g newborn, no abnormality
4	Non-reactive	Non-reactive	G_1P_0 38^{+2} weeks, admitted and cesarean delivery on the same day, thick meconium-stained AF, 2,690 g newborn, no abnormality
5	Non-reactive	Reactive	G_4P_3 40^{+3} weeks, induced labor at 41^{+3} and cesarean delivery due to failed induction, healthy 3,240 g newborn, no abnormality
6	Non-reactive	Reactive	G_1P_0 38^{+3} weeks, continued pregnancy until normal vaginal delivery at 38^{+5} weeks, healthy 2,720 g newborn, no abnormality
7	Non-reactive	Non-reactive	G_2P_1 37^{+3} weeks, BPP 8/10 then reactive NST on the same day, continued pregnancy until normal vaginal delivery at 38^{+3} weeks, healthy 2,920 g newborn, no abnormality
8	Non-reactive	Non-reactive	$G_3P_{/2}$ 33^{+3} weeks, BPP 8/10 then reactive NST on the same day, continued pregnancy until normal vaginal delivery at 37^{+5} weeks, healthy 2,990 g newborn, no abnormality
9	Non-reactive	Reactive	G_2P_1 37^{+6} weeks, continued pregnancy until normal vaginal delivery at 39^{+5} weeks, healthy 3,360 g newborn, no abnormality
10	Non-reactive	Non-reactive	$G_3P_{/2}$ 35^{+1} weeks, BPP 8/10 then reactive NST on the same day, continued pregnancy until normal vaginal delivery at 39^{+5} weeks, healthy 3,290 g newborn, no abnormality
11	Non-reactive	Non-reactive	$G_3P_{/2}$ 33^{+4} weeks, BPP 8/10 then reactive NST on the same day, continued pregnancy until normal vaginal delivery at 37^{+5} weeks, healthy 2,900 g newborn, no abnormality
12	Reactive	Non-reactive	$G_4P_2A_1$ 34^{+5} weeks, continued pregnancy until normal vaginal delivery at 39^{+2} weeks, healthy 3,190 g newborn, no abnormality
13	Non-reactive	Reactive with variable deceleration 1 time	G_1P_0 38^{+1} weeks, continued pregnancy, diagnosed preeclampsia with severe features at 38^{+5} weeks, cesarean delivery due to failed induction, healthy 2,440 g newborn, no abnormality

NST: non-stress test, BPP: biophysical profile scores, g: grams, AF: amniotic fluid

Lastly, Table 5 presents the median and interquartile ranges (IQR) of VAS level scores showing the participants' discomfort feeling at the 5^{th}, 15^{th}, and 20^{th} minute without and with face mask wearing. The median and IQR of VAS level scores of participants' discomfort feeling at the 5^{th},

15th, and 20th minute were significantly higher when wearing a face mask than when not wearing a face mask [0.95 (0.15-2.75) vs 0.15 (0-1.8), 0.9 (0.2-2.65) vs 0.35 (0-1.8) and 1.0 (0.1-2.9) vs 0.4(0.1-1.35) cm, p = 0.002, 0.003, and 0.003, respectively)].

Table 5. The median (interquartile ranges) of visual analogue scale level of participants' discomfort feeling at the 5th, 15th, and 20th minutes without and with face mask wearing.

	Without face mask wearing	With face mask wearing	p value
VAS (cm)			
at 5th minute	0.15 (0–1.8)	0.95 (0.15–2.75)	0.002
at 15th minute	0.35 (0.1–1.8)	0.9 (0.2–2.65)	0.003
at 20th minute	0.4 (0.1–1.35)	1.0 (0.1–2.9)	0.003

* Wilcoxon signed-rank.
VAS: visual analogue scale, cm: centimeters

Discussion

A significant lowering of mean maternal oxygen saturation was observed at the 5th minute in the healthy pregnant women when wearing a face mask compared to at the same time when not wearing a face mask. We hypothesized that this was related to a reduction in oxygen uptake by the barrier function of the face mask and aggravated by CO_2 accumulation occurring beneath the face mask. This finding was similar to in the previous study that evaluated surgeons' oxygen saturation levels before and after wearing a surgical face mask during performing major operations. The study found that surgeons' oxygen saturation decreased after the first hour of surgical mask wearing, especially in surgeons older than 35 years old. Moreover, the level of oxygen saturation decrease was found to be greater in longer times[10]. For pregnant women, previous studies found that oxygen saturation was significantly reduced, especially when using double surgical mask[11, 12]. Fortunately, the significant lowering of maternal saturation was revealed only at the 5th minute with face mask wearing, while the mean maternal oxygen saturation was not significantly different for participants with and without face mask wearing at the 15th and 20th minutes. Thus, healthcare providers can be reassured about the safety of face mask wearing in the context of the level of maternal oxygen saturation for avoiding COVID-19 spreading in healthy pregnant women. However, the physiologic mechanism that the pregnant woman uses to compensate for the oxygenation reduction is still unclear. The maternal respiratory rate and heart rate in our study did not show any significant differences in the cases without and with face mask wearing. Possibly, temporary deep breathing may be induced in the pregnant women in the first 5 minutes of face mask wearing.

A significant reduction of the mean diastolic blood pressure was observed in the healthy pregnant women at the 5th minute with face mask wearing compared to at the 5th minute without face mask wearing. This finding contrasted with a previous study that monitored the maternal heart rate, blood pressure, mean arterial blood pressure, total peripheral resistance, stroke volume, and oxygen saturation between pregnant and non-pregnant women with and without wearing an N95 filtering face piece respirator. That study found that diastolic blood pressure was significantly increased in both pregnant and non-pregnant women, but not differently between the pregnant and non-pregnant women. That different finding compared to our study may be explained by

the different gestational age of the participants and differences in the activities between both studies. Anyway, the physiological response to the diastolic blood pressure changing remains unclear[13].

The incidence of non-reactive NST in our study was 6.9%, which was lower than in many other studies, probably because our participants were healthy pregnant women. Most the NST in previous studies were performed in high-risk pregnancies. The true positive rate and specificity true negative rate of NST in this study were 20% and 94%, respectively. The rates were comparable with previous studies[14, 15]. Fortunately, non-reactive NST results were comparable in both groups. Moreover, most of the non-reactive NST results in our study were false-positive tests. We hypothesized that the duration and difference in the sleep–wake cycle in individual fetuses may explain this finding, not directly reasoned by the face mask wearing effect. Anyway, the limitation of the study was our number of sample size may be not enough to answer the effect of face mask wearing to NST. The duration of NST has been found to influence the appearance and the relative percentage of fetal reactivity during the NST. A longer NST time increased the rate of reactive NST. We plan to perform a further cross study in which participants will be introduced to NST with face mask wearing before NST is performed without face mask wearing[16]. Moreover, other fetal well-being assessments should be additionally performed for reassurance of the fetal status. Finally, a feeling of discomfort was significantly presented by the pregnant women in our study. Despite this, face mask wearing is a strongly effective method for preventing the spread of COVID-19. Thus, healthcare providers should be aware of potential feelings of discomfort which could affect the mask wearing status and should encourage all healthy pregnant women to wear a face mask at all times when other social distancing measures are difficult to adhere to. There are many face mask types. We plan to evaluate the maternal response to other types of face mask in a further study. Moreover, we plan to perform a cross sectional study to evaluate the rate of non-reactive NST by monitoring the NST results in participants with wearing a mask first, and then without wearing a mask. The current study is the first to evaluate the effect of face mask wearing on maternal oxygen saturation and other vital signs and also its effect on NST results interpretation during the current COVID-19 pandemic. The reduction of the diastolic blood pressure found at the 5th minute in participants with face mask wearing could not be clearly explained by the pathogenesis. Although mean maternal oxygen saturation and diastolic blood pressure were statistically significantly lower at the 5th minute of monitoring the pregnant women when wearing a face mask than at the 5th minute when not wearing a face mask, these may not be clinically significant.

Conclusion

In conclusion, it was evident that the mean maternal oxygen saturation and maternal diastolic blood pressure were significantly lower in participants at the 5th minute of being monitored when wearing a face mask than at the 5th minute in participants not wearing a face mask, but no differences were found when monitoring for a longer time. Non-reactive NST results are comparable when wearing and not wearing a face mask. The pregnant women also significantly presented a feeling of discomfort when wearing the face mask compared to when not wearing the face mask.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Effect of Video-based Educational Tool about Pertussis on the Decision to Receive Pertussis Vaccine during Pregnancy

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ABSTRACT

Objectives: To assess the impact of a video on pertussis vaccination intentions among pregnant women and identify factors influencing their decision-making.

Materials and Methods: This quasi-experimental study was conducted from June to August 2023. Participants were pregnant women between 27 and 36 weeks of gestation. Both intervention and control groups received standard prenatal care and completed a questionnaire. The intervention group additionally watched a video on the pertussis vaccine and repeated the questionnaire.

Results: A total of 80 participants were enrolled, with 41 in the intervention group and 39 in the control group. The groups were similar in characteristics except for gestational age (29.78 ± 2.34 vs 31.69 ± 2.45 weeks, $p < 0.001$). Vaccination decision-making did not differ significantly between groups ($p = 0.624$), though the intervention group showed higher post-video knowledge scores (6.48 ± 1.62 vs 7.19 ± 1.05, $p = 0.022$). The intervention group exhibited a 42% increase in vaccination intentions, particularly among initially undecided participants. Key factors influencing increased vaccine acceptance in the intervention group included improved knowledge, safety concerns, cost, and medical personnel recommendations.

Conclusion: Viewing the video increased vaccination intentions by 42%, particularly among women who were initially uncertain about vaccination.

Keywords: pertussis vaccine, pregnancy, vaccination intentions, decision making, video intervention.

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ผลของการรับชมวิดีโอเรื่องวัคซีนป้องกันโรคไอกรน ต่อการเข้ารับวัคซีนป้องกันโรคไอกรนในหญิงตั้งครรภ์

รุจยา สุริยะจันทร์, สิริพร ไตรนาค

บทคัดย่อ

วัตถุประสงค์: *วิดีโอเรื่องวัคซีนป้องกันโรคไอกรน เพื่อส่งเสริมการฉีดวัคซีนป้องกันโรคไอกรนในหญิงตั้งครรภ์และค้นหาปัจจัยที่มีผลต่อการเข้ารับวัคซีนในหญิงตั้งครรภ์*

วัสดุและวิธีการ: *การวิจัยกึ่งทดลอง (Quasi-Experimental design) มีกลุ่มทดลองและกลุ่มควบคุม เก็บข้อมูลในเดือนมิถุนายน ถึงเดือนสิงหาคม 2566 ผู้เข้าร่วมวิจัยทั้งหมดเป็นหญิงตั้งครรภ์ในช่วงอายุครรภ์ 27 ถึง 36 สัปดาห์ ทั้งสองกลุ่มจะได้รับการรักษาตามมาตรฐาน และทำแบบสอบถาม โดยกลุ่มทดลองจะได้รับชมวิดีโอเรื่องวัคซีนป้องกันโรคไอกรน และทำแบบสอบถามซ้ำอีกครั้ง*

ผลการศึกษา: *จากผู้เข้าร่วมงานวิจัยทั้งหมด 80 ราย แบ่งเป็นกลุ่มทดลอง 41 ราย และกลุ่มควบคุม 39 ราย ลักษณะของกลุ่มประชากรไม่มีความแตกต่างกันทางสถิติ ยกเว้นอายุครรภ์ (29.78 ± 2.34 vs 31.69 ± 2.45 สัปดาห์ ($p < 0.001$) เมื่อเปรียบเทียบระหว่างกลุ่มควบคุมและกลุ่มทดลองหลังรับชมวิดีโอพบว่า การตัดสินใจรับวัคซีนนั้นไม่แตกต่างกัน ($p = 0.624$) แม้ว่ากลุ่มทดลองหลังรับชมวิดีโอจะมีคะแนนความรู้มากกว่าก็ตาม (6.48 ± 1.62 vs 7.19 ± 1.05 คะแนน, $p = 0.022$) อย่างไรก็ตามในกลุ่มทดลองก่อนและหลังรับชมวิดีโอ พบว่ามีการตัดสินใจฉีดวัคซีนเพิ่มขึ้นร้อยละ 42 ในผู้เข้าร่วมที่ยังไม่ตัดสินใจก่อนรับชมวิดีโอ ซึ่งปัจจัยที่มีผลต่อการตัดสินใจรับวัคซีนเพิ่มขึ้น ได้แก่ ความรู้, ความปลอดภัย, ราคา และคำแนะนำ*

สรุป: *วิดีโอเพิ่มอัตราการตัดสินใจฉีดวัคซีน ในกลุ่มทดลองที่ไม่แน่ใจในการฉีดวัคซีนได้ร้อยละ 42*

คำสำคัญ: *วัคซีนไอกรน, คนท้อง, ตั้งครรภ์, วิดีโอ*

Introduction

Pertussis, or whooping cough, is caused by the bacterium Bordetella pertussis and spreads through airborne droplets. Initially, symptoms resemble those of a cold, but chronic coughing may persist for months or progress to respiratory exhaustion. In children, symptoms can be more severe compared to adults, and children are more likely to require hospitalization[1, 2, 3]. Therefore, it is important to promote pertussis vaccination to prevent infection and reduce disease severity, especially in vulnerable populations such as children, unimmunized adults and pregnant women[4, 5]. The Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG) recommend the pertussis vaccine for pregnant women between 27 and 36 weeks of gestation to develop and transfer maternal immunity to their babies[6, 7].

Currently, the rate of pertussis vaccination among pregnant women remains low. In Thailand, there is a lack of clear statistical data regarding the uptake of pertussis vaccination among pregnant women. At Chonburi Hospital, the initiative to distribute pertussis vaccines began in September 2022, with an average of 20 vaccinations administered per month. At the time of this research, the cost of administering the pertussis vaccine to pregnant women was approximately 400 baht for all patients.

Recognizing the low vaccination rates, previous research[8-12] aimed to improve vaccination rates and found that pregnant women were more likely to intend to receive the vaccine after being encouraged by a healthcare provider. Moreover, a study by Chamberlain AT et al[13] proposed that healthcare providers' vaccine recommendations are one of the key factors influencing maternal vaccine acceptance. Subsequently, Chamberlain AT developed evidence-based video tutorials for healthcare providers to improve their confidence in discussing vaccination with pregnant women.

A previous study by Ratanasaengsuang A[8] used prenatal classes as a tool to promote the pertussis vaccine among pregnant women. On the other hand, this approach was not feasible for Chonburi Hospital due to the large number of pregnant women seeking services and the limited staff availability at the antenatal care clinic.

In our study, we developed an informative video as a direct communication tool. The goal was to provide comprehensive and sufficient information to pregnant women during their antenatal clinic visits, without disrupting the service management of the obstetrics department.

The objective of this study was to compare the decision rate for receiving the vaccine and related factors after watching an educational video about the pertussis vaccine.

Materials and Methods

This research was a single center, non-blinded, quasi-experimental study conducted at Chonburi Hospital, a tertiary care facility within the Region 6 Health Provider, Thailand. The study was carried out from June 2023 to August 2023. The Institutional Review Board of the Chonburi Hospital Medical Education Center granted ethical approval for the study under a waiver of informed consented (reference number 23/66/R/h3).

All pregnant women who visited the obstetrics department at Chonburi Hospital from June to August 2023, with gestational ages ranging from 27 to 36 weeks (confirmed by ultrasound before 22 weeks), who had not received a prior pertussis vaccination, and who were able to read and understand the Thai language were eligible for the study. Those who met the inclusion criteria were invited to participate, and informed consent was obtained by nurses or nurse aides. If any participant had questions about the research, they could inquire about the procedures from the department staff or contact the researchers directly. Participants had the option to withdraw from the research at any time without affecting their standard of care.

After informed consent was obtained, participants were assigned to either the intervention or control group based on the timing of their visit to the antenatal clinic, as the video was presented during antenatal clinic sessions starting in July 2023. Participants who visited the antenatal clinic from June to July 2023 were assigned to the control group, while those who visited after July 2023 were assigned to the intervention group. The study was not blinded after the assignment of the two groups. Both the intervention and control groups underwent standard prenatal examinations conducted by physicians in the obstetrics department and were provided with a questionnaire to collect essential information. The developed and validated questionnaire consisted of three parts. The first part collected personal and pregnancy history. The second part included 10 true-or-false questions, with a total score of 10, designed to assess participants' baseline knowledge about pertussis disease and the pertussis vaccine. The final part assessed whether participants agree that knowledge, safety, cost, and advice influence their decision-making regarding pertussis.

Upon completion of the questionnaire, the intervention group had to watch an educational video at a designated location. The video, which was reviewed and approved by three staff members from the Maternal-Fetal Medicine (MFM) department, was approximately three minutes long and provided information about pertussis disease and vaccine recommendations. Following the video, participants in this group were asked to repeat the questionnaire again.

Participants interested in receiving the pertussis vaccination were given a prescription by a physician, then purchased the vaccine from the pharmacy department at Chonburi Hospital and returned to the obstetrics department to have the vaccine administered by a nurse. Following the vaccination, participants were required to remain under observation by the nurse for at least 30 minutes to monitor for any allergic reactions or adverse effects before being allowed to return home.

The primary outcome was to evaluate the effect of the video on receiving the pertussis vaccine among pregnant women. The secondary outcome was to identify factors associated with vaccination decision-making, such as knowledge, safety concerns, cost, and recommendations from medical personnel.

Based on previous research conducted by Ratanasaengsuang A[8], which employed a cross-sectional descriptive study design, a significant increase in interest in receiving the pertussis vaccination was observed, rising from 45.5% to 81.9% after participants received advice from obstetricians in the Department of Obstetrics. This difference was statistically significant, achieving 90% study power with a p value of < 0.05. The sample size for this research was calculated using the two independent proportions method, determining a sample size of $n = 27$ individuals per group. To account for potential dropouts before the study's conclusion, estimated at approximately 20%, a total of 64 participants were enrolled in the study. These participants were evenly divided into intervention and control groups, with each group comprising 32 individuals.

The normal distribution of variables was assessed using the Shapiro-Wilk test. Data analysis was performed using Stata Version 16 and the R statistical program, with the data categorized into two types for analysis. First, for quantitative data such as age, number of pregnancies, and scores on knowledge among the intervention and control groups, calculations were done using the independent t test, while the scores on knowledge within the intervention group before and after watching the video were calculated using the paired t test. Second, for qualitative data such as vaccination rates, factors influencing

vaccination decisions, education levels, and monthly incomes, comparisons between the intervention and control groups were made using the chi square or Fisher exact test. Within the intervention group, differences in qualitative data between pre- and post-intervention were assessed using the Stuart-Maxwell test for marginal homogeneity.

Results

A total of 85 participants were assessed for eligibility, out of which 80 were enrolled in trial, with 39 assigned to the control group and 41 to the intervention group (Fig.1). Baseline characteristics of the control and intervention groups regarding general information such as age, education level, monthly income, general knowledge scores related to pertussis, and factors influencing vaccination decisions did not statistical significance, except for gestational age (Table 1). The average gestational age in the control group was 31.69 ± 2.45 weeks, whereas in the intervention group it was 29.78 ± 2.34 weeks ($p < 0.001$). Additionally, there was a trend towards more vaccination decisions in the control group with 28 individuals deciding to vaccinate, compared to 21 in the intervention group. However, the difference in the number of individuals deciding to vaccinate did not reach statistical significance ($p = 0.088$).

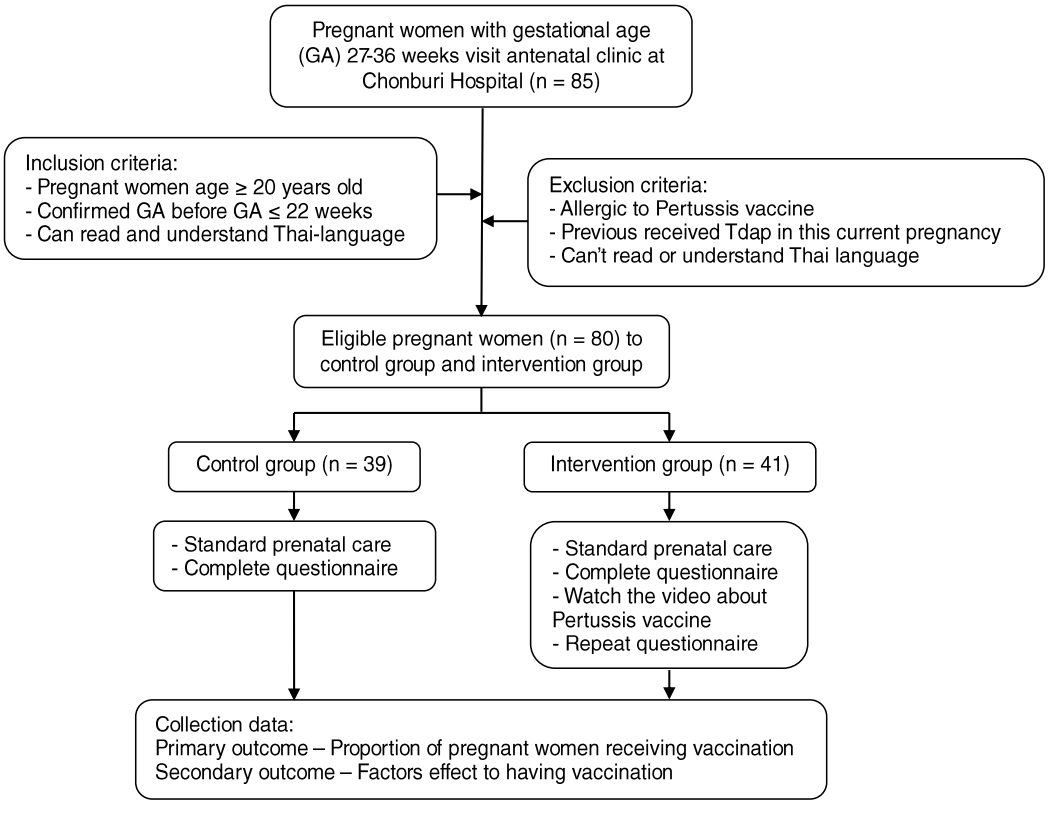

Fig. 1. Flow diagram.
Tdap: tetanus, diphtheria, and acellular pertussis

Table 1. Baseline characteristics.

	Control group (n = 39)	Intervention group (n = 41)	p value
Age (mean ± SD)	29.41 ± 5.93	27.68 ± 5.49	0.180
GA (mean ± SD)	31.69 ± 2.45	29.78 ± 2.34	< 0.001
Education, n (%)			0.385
Less or elementary	6 (15.38)	5 (12.20)	
High school	17 (43.59)	18 (43.90)	
Diploma	8 (20.51)	14 (34.15)	
More or bachelor	8 (20.51)	4 (9.76)	
Income, n (%)			0.920
< 10,000	13 (33.33)	12 (29.27)	
10,000 - 20,000	24 (61.54)	27 (65.85)	
20,001 - 30,000	2 (5.13)	2 (4.88)	
Score (mean ± SD)	6.48 ± 1.62	6.58 ± 1.39	0.772
Knowledge, n (%)			0.417
Agree	29 (74.36)	25 (60.98)	
Not sure	9 (23.08)	15 (36.59)	
Disagree	1 (2.56)	1 (2.44)	
Safety (n,%)			0.256
Agree	31 (79.49)	26 (63.41)	
Not sure	7 (17.95)	14 (34.15)	
Disagree	1 (2.56)	1 (2.44)	
Cost, n (%)			0.603
Agree	24 (61.54)	21 (51.22)	
Not sure	12 (30.77)	17 (41.46)	
Disagree	3 (7.69)	3 (7.32)	
Advise, n (%)			0.342
Agree	32 (82.05)	30 (73.17)	
Not sure	7 (17.95)	11 (26.83)	
Disagree	0	0	
Decision, n (%)			0.088
Agree	28 (71.79)	21 (51.22)	
Not sure	9 (23.08)	19 (46.34)	
Disagree	2 (5.13)	1 (2.44)	

SD: standard deviation

Table 2 presents the primary and secondary outcomes of this research. There were no statistically significant differences in the intention to receive the vaccine or the factors influencing vaccination decisions between the control group and the post-intervention group, except for the factor related to knowledge (p = 0.014). Even though the knowledge score in the post-intervention group was significantly higher than that in the control group (6.48 ± 1.62 vs 7.19 ± 1.05, p = 0.022), and the factor related to knowledge differed significantly between these groups (p = 0.014). The number of individuals deciding to receive the vaccine did not differ between these groups (71.79% vs 68.29%, p = 0.624). Similarly, factors influencing vaccination decisions such as safety concerns, cost considerations, and recommendations from medical personnel, did not differ between groups.

Table 2. Outcome and factors effect to decision.

Variable	Control	Post-intervention	p value
Score (mean ± SD)	6.48 ± 1.62	7.19 ± 1.05	0.022
Knowledge, n (%)			0.014
Agree	29 (74.36)	39 (95.12)	
Not sure	9 (23.08)	2 (4.88)	
Disagree	1 (2.56)	0	
Safety, n (%)			0.882
Agree	31 (79.49)	34 (82.93)	
Not sure	7 (17.95)	7 (17.07)	
Disagree	1 (2.56)	0	
Cost, n (%)			0.313
Agree	24 (61.54)	26 (63.41)	
Not sure	12 (30.77)	8 (19.51)	
Disagree	3 (7.69)	7 (17.07)	
Advise, n (%)			0.167
Agree	32 (82.05)	36 (87.80)	
Not sure	7 (17.95)	3 (7.32)	
Disagree	0	2 (4.88)	
Decision, n (%)			0.624
Agree	28 (71.79)	28 (68.29)	
Not sure	9 (23.08)	8 (19.51)	
Disagree	2 (5.13)	5 (12.20)	

SD: standard deviation

However, when comparison within the intervention group before and after watching the pertussis vaccine video revealed a statistically significant increase in vaccination decisions after the

intervention (Table 3). In pre-intervention group, 21 participants (51.22%) decided to receive the vaccine, whereas post-intervention, 28 participants (68.29%) decided to receive it (p = 0.017). Regarding the secondary outcomes, factors influencing vaccination decisions differed significantly after watching the video. All of these factors included knowledge (60.98% vs 95.12%, p = 0.002), safety (63.41% vs 82.93%, p = 0.039), cost (51.22% vs 63.41%, p = 0.031), and recommendations from medical personnel (73.17% vs 87.80%, p = 0.018). These findings suggested that the intervention of watching the video significantly improved participants' decision-making about pertussis vaccination, especially among those who were hesitant or undecided. The vaccination rate in this subgroup increased by 42%, indicating the video's effectiveness in addressing concerns related to knowledge, safety, cost, and recommendations from medical personnel.

Table 3. Outcome and factors effect to decision in intervention group.

Variable	Pre-intervention	Post-intervention	p value*
Score (mean ± SD)	6.58 ± 1.39	7.19 ± 1.05	0.005
Knowledge, n (%)			0.002
Agree	25 (60.98)	39 (95.12)	
Not sure	15 (36.59)	2 (4.88)	
Disagree	1 (2.44)	0	
Safety, n (%)			0.039
Agree	26 (63.41)	34 (82.93)	
Not sure	14 (34.15)	7 (17.07)	
Disagree	1 (2.44)	0	
Cost, n (%)			0.031
Agree	21 (51.22)	26 (63.41)	
Not sure	17 (41.46)	8 (19.51)	
Disagree	3 (7.32)	7 (17.07)	
Advise (n,%)			0.018
Agree	30 (73.17)	36 (87.80)	
Not sure	11 (26.83)	3 (7.32)	
Disagree	0	2 (4.88)	
Decision (n,%)			0.017
Agree	21 (51.22)	28 (68.29)	
Not sure	19 (46.34)	8 (19.51)	
Disagree	1 (2.44)	5 (12.20)	

SD: standard deviation

Discussion

Our study found no statistically significant difference in vaccination intentions when comparing the control group and the post-intervention group. Moreover, the factors influencing vaccination decisions did not differ between the groups, with the exception

of knowledge.

In a previous trial, the intention to receive the pertussis vaccination during pregnancy was increased by providing information[8-10,12] and demonstrating that using video as a tool can effectively address informational needs[11, 13]. However, our study using a video as the intervention showed no statistically significant difference in vaccination intentions. This may be due to the intervention group being less likely to receive the vaccine prior to viewing the video, which could have influenced the comparison between the control and post-intervention groups, resulting in no significant difference. Nevertheless, a significant difference was observed between the pre-and post-intervention groups. Within the intervention group, there was a statistically significant increase in vaccination intentions, along with notable changes in certain factors influencing vaccination decisions, including knowledge, safety, cost, and recommendations from medical personnel.

According to the questionnaire design, the third part of the questionnaire, which evaluated the factors related to vaccine decision-making, used a closed-ended question format to minimize disruption to participants. However, a limitation of using closed-ended questions with options such as 'agree,' 'not sure,' and 'disagree' was that it did not provide a clear understanding of the underlying reasons, which could have been important for identifying modifiable factors to increase vaccination intentions.

In the case of the informative video, we found that the increase in knowledge scores did not influence vaccination decision-making. This indicated that the video content not only provided information but also emphasized the importance of vaccination. Although an informative video may seem able to replace individual counseling in an antenatal clinic and ensure that every pregnant woman receives complete and sufficient information, it is a one-way form of communication. Due to the protocol of this research, we set up the video to be watched after the antenatal care visit to reduce bias from the doctor's advice. However, to enhance vaccination rates, watching the video before seeing the doctor and having a discussion as part of a two-way communication approach may increase the intention to receive vaccination.

Using an informative video combined with recommendations from healthcare providers may effectively increase the intention to receive vaccination. However, cost is also a key influencing factor in vaccine decision-making, often leading to limited vaccine affordability. As a result, providing free pertussis vaccines to all pregnant women may further increase vaccination intentions. Moreover, some pregnant participants were unable to decide about receiving the vaccine immediately after watching the video. Giving them more time to discuss with their families, make a decision at their next appointment, or providing sufficient financial support might increase their vaccination intentions.

Therefore, it can be concluded that among pregnant women who already intended to receive the pertussis vaccination, watching an educational video did not significantly increase vaccination rates. However, for those uncertain or undecided, viewing the video increased vaccination rates by 42%. Furthermore, factors that can be altered to increase vaccination rates among the group of individuals who are undecided include giving knowledge and receiving recommendations from medical personnel regarding the advisability of receiving pertussis vaccination during pregnancy.

A strength of this study was the use of video as a tool to promote pertussis vaccination, which had not been attempted before. The advantage of using video is that it ensures all pregnant women receive equal and sufficient knowledge, while also reducing the workload for healthcare providers. This approach is particularly suitable for hospitals with high patient volumes or limited medical staff. In the future, this video could be further developed and implemented in other hospitals, or adapted to provide information on other topics for patients.

However, our study had several limitations. Firstly, it was conducted at a single center with a small

sample size. Secondly, the study did not use randomization or blinding after assigning the intervention. Future research involving a larger sample size and utilizing a randomized controlled trial design may reveal significant differences in vaccination intentions between the control and post-intervention groups. Thirdly, the video was limited to individuals who could understand and read the Thai language. Finally, after the Thai Department of Disease Control[14] released its updated pertussis vaccine recommendation, which revised the gestational age for vaccination from 20 to 32 weeks of pregnancy and offered the vaccine free of charge, this change could impact the intention of Thai pregnant women to receive the pertussis vaccine. Further studies should evaluate the vaccination rate following the implementation of this recommendation.

Conclusion

Our quasi-experimental study showed no effect of watching a video on enhancing the intention to receive the pertussis vaccine among pregnant women with a gestational age of 27 to 36 weeks. However, viewing the video increased vaccination intentions by 42%, particularly among women who were initially uncertain about vaccination.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Effects of Local Lidocaine Spray with Intravenous Meperidine for Pain Relief during Manual Vacuum Aspiration: A double-blinded placebo controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of local cervical lidocaine spray with intravenous meperidine for pain relief during the manual vacuum aspiration (MVA) procedure compared to a local placebo spray with intravenous meperidine.

Materials and Methods: A randomized, double-blinded, placebo-controlled trial was conducted in a tertiary care center during December 2023 to August 2024. 216 patients who underwent the MVA procedure and met the inclusion criteria participated in the trial, with 108 randomly assigned to the 10% lidocaine spray group and another 108 to the placebo group. A pharmacist prepared the packaging of topical spray for both groups to be identical. The intravenous analgesic agents used for pain relief were the same in both groups. The primary outcome was to compare pain scores using the visual analog scale during MVA between groups. The secondary outcome was to evaluate the side effects of the local lidocaine spray.

Results: The baseline characteristics were not different in both groups. The mean immediately post MVA pain score in the lidocaine spray group was significant less than the placebo group (1.62 ± 2.10 and 2.37 ± 2.43 respectively; mean difference 0.75; 95% confidence interval 0.13-1.36, p = 0.016). However, there was no significant difference in pain score at the time before the operation, during the tenaculum application, during the MVA procedure, and 30 minutes post-MVA between two groups. There were no serious side effects in both groups.

Conclusion: Lidocaine spray could effectively reduce the pain at immediately post MVA without any serious side effects. It can be used as the additional therapy for pain reducing in the MVA procedure.

Keywords: manual vacuum aspiration, lidocaine spray, pain score, anesthesia, pain control.

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ผลของยาลิโดเคนแบบพ่นฝอยเฉพาะที่ร่วมกับเมเพอริดีนทางหลอดเลือดดำในการช่วยลดระดับความเจ็บปวดขณะทำหัตถการขูดหรือดูดโพรงมดลูกด้วยเครื่องสุญญากาศ: การศึกษาควบคุมด้วยยาหลอกและปกปิดสองทาง

ภัทริกาญจน์ มานะยิ่ง, โชคชัย โชติบูรณ์, อุดมลักษณ์ รังสิยาภรณ์รัตน์, ศรีสุดา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิภาพในการลดปวดของการใช้ยาลิโดเคนพ่นฝอยบริเวณปากมดลูกร่วมกับเมเพอริดีนทางหลอดเลือดดำขณะทำหัตการดูดโพรงมดลูกด้วยเครื่องสุญญากาศเปรียบเทียบกับการพ่นยาหลอกบริเวณปากมดลูกร่วมกับเมเพอริดีนทางหลอดเลือดดำ*

วัสดุและวิธีการ: *การวิจัยชนิดการศึกษาทดลองแบบสุ่มปกปิด 2 ทาง ในโรงพยาบาลตติยภูมิ ตั้งแต่ธันวาคม 2566 ถึงสิงหาคม 2567 โดยเก็บข้อมูลจากผู้ป่วย 216 ราย ที่เข้ารับการรักษาด้วยการทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศ เข้าเกณฑ์การคัดเลือกจะถูกจัดสรรให้อยู่ในกลุ่มหนึ่งจากสองกลุ่ม ได้แก่กลุ่มที่ได้รับยาลิโดเคนพ่นฝอยขนาดความเข้มข้นร้อยละ 10 ที่บริเวณปากมดลูก (จำนวน 108 ราย) และกลุ่มที่ได้รับยาหลอก (จำนวน 108 ราย) โดยทั้งสองกลุ่มได้รับการฉีดพ่นสเปรย์ที่มีบรรจุภัณฑ์เหมือนกันซึ่งถูกจัดเตรียมโดยเภสัชกร และทั้งสองกลุ่มใช้ยาระงับปวดทางหลอดเลือดดำชนิดเดียวกัน ผลลัพธ์หลัก คือการเปรียบเทียบระดับค่าคะแนนความปวดด้วยมาตรวัดความปวดด้วยสายตาขณะทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศระหว่างกลุ่ม ผลลัพธ์รอง คือการประเมินผลข้างเคียงของยาลิโดเคนพ่นฝอยบริเวณปากมดลูก*

ผลการศึกษา: *พบว่าข้อมูลพื้นฐานของทั้งสองกลุ่มไม่ได้มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ คะแนนความปวดเฉลี่ยหลังจากทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศทันทีพบว่ากลุ่มที่ได้รับยาลิโดเคนพ่นฝอย มีค่าความปวดลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มยาหลอก (ค่าเฉลี่ยความปวด 1.62 ± 2.10 และ 2.37 ± 2.43; ความแตกต่างค่าเฉลี่ย 0.75; ช่วงเชื่อมั่นร้อยละ 95 0.13 ถึง 1.36 p = 0.016) อย่างไรก็ตาม ไม่มีความแตกต่างอย่างมีนัยสำคัญในคะแนนความปวดระหว่างสองกลุ่มในช่วงก่อนการผ่าตัด ขณะใส่อุปกรณ์หนีบปากมดลูก ขณะทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศ และหลังการทำหัตถการ 30 นาที และไม่พบผลข้างเคียงร้ายแรงในทั้งสองกลุ่ม*

***สรุป**: ยาลิโดเคนพ่นฝอยสามารถลดความเจ็บปวดหลังทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศทันที โดยไม่มีผลข้างเคียงร้ายแรง จึงสามารถพิจารณาใช้เป็นการรักษาเพิ่มเติมเพื่อช่วยลดความเจ็บปวดในการทำหัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศได้*

***คำสำคัญ**: หัตถการดูดโพรงมดลูกด้วยเครื่องสุญญากาศ, ยาลิโดเคนแบบพ่นฝอย, ระดับความปวด, การดมยาสลบ,การลดความปวด*

Introduction

Manual vacuum aspiration (MVA) is a frequently used gynecological procedure in various conditions, such as abnormal uterine bleeding and termination of pregnancy[1, 2]. Pain during MVA procedure may be caused by several factors, such as cervical pain from cervical dilatation, uterine contractions, and anxiety during the procedure[3]. The average pain score by visual analogue scale during the MVA procedure is about 4-5[4]. However, a study reported that 78.5% of cases experienced severe pain (pain score ≥ 7) during the procedure, despite the use of intravenous opioids for pain relief[5].

There are various methods to reduce pain during MVA. Nonsteroidal anti-inflammatory drugs, opioids, local anesthesia, and general anesthesia are commonly used in different ways according to each healthcare center's protocols[3, 5-8]. Lidocaine is frequently used as a local analgesic, such as in a paracervical block[9] which is a common method to reduce pain during cervical and uterine procedures. Nevertheless, it can cause some serious side effects after application such as nausea, vomiting, dizziness, unstable vital signs or death[8, 10]. On the other hand, the application of local cervical lidocaine spray has been reported to have good efficacy, in endometrial sampling procedures (such as Endocell®, Pipelle®, and Novak curettage®)[11-13] and intrauterine device insertion[14, 15], with fewer complications[16, 17]. Cervical lidocaine spray method became more convenient and safer when compared to the paracervical block technique[17].

However, the effectiveness of local cervical lidocaine spray in MVA procedures has not been studied. Therefore, this study aimed to evaluate the effectiveness of local cervical lidocaine spray combined with intravenous analgesics for pain relief during the MVA procedure compared to intravenous analgesics with placebo.

Materials and Methods

This study is a randomized, double blinded, placebo-controlled trial conducted at Udonthani Hospital, a tertiary care center, Thailand.

The inclusion criteria was the women aged 20-60 years, who had an indication for MVA procedure[4]. The exclusion criteria were allergy or hypersensitivity to lidocaine, having symptoms of reproductive tract infection or urinary tract infection, having abnormal vital signs, having chronic liver or kidney diseases. Study methods

The study details were explained to the participants and the written informed consent was obtained before their participation. The randomization was performed sequentially by computer generated numbers, prepared in sealed, opaque envelopes. The eligible patients were randomly assigned into two groups by the researchers. Group 1 received 4 puffs of 10% lidocaine spray without adrenaline, while group 2 received 4 puffs of placebo (normal saline with the similar packaging)

The MVA procedure was performed at the gynecological ward, with basic characteristics and

associated factors collected in the case record form. Participants were positioned in the dorsal lithotomy position. Fifteen to twenty minutes before the operation, 50 milligrams of intravenous meperidine was administered for analgesia. The skin was cleaned with povidone iodine solution, and a sterile cloth was applied. A speculum was inserted, and the vagina was cleaned again with povidone iodine solution. Lidocaine spray (10% lidocaine spray without adrenaline) or placebo (normal saline spray) was applied with four puffs on the cervix. Pain score was assessed using a 10 cm visual analogue scale (VAS), where participants rated their pain from 0 (no pain) to 10 (worst pain)[18]. These ratings were recorded on the scale. A tenaculum was then clamped at the 2 and 10 o'clock positions on the cervix, and the pain score was assessed again.

Next, the length of the uterine cavity was measured using a uterine sound. A Karman cannula with a vacuum syringe was used to aspirate the endometrial tissue, with the size of the cannula selected based on the cervical os. The participants assessed their pain score immediately at each step. After completing the procedure, the bleeding was checked, and the device was removed. The overall pain score was assessed once more immediately after the procedure and then reassessed at 30 minutes post-procedure. Side effects, such as nausea, vomiting, hypotension, abnormal bleeding (estimated > 250 mL), dizziness, and perineum itching, were recorded. The summary of the pain assessment time points is presented in Fig. 1.

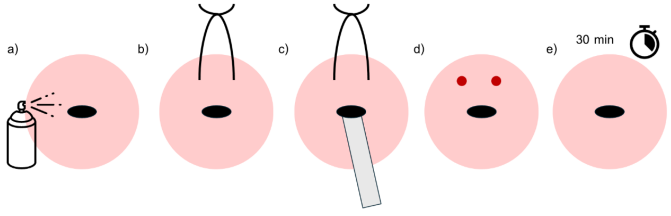

Fig. 1. Steps of pain assessment in this study.

All eligible participants were informed about the study's purpose, procedures, potential risks, and benefits before providing written informed consent. Participants voluntarily agreed to participate without any monetary compensation. They received guidance and information about the procedure, including possible discomfort or side effects, such as mild pain or adverse reactions to medication.

In order to ensure confidentiality in the data collection, the subject identification code was used in the case record form. The information was recorded, entered into Stata file, and was analyzed.

Both patients and investigators were blinded in this study. The lidocaine spray and placebo were prepared by a pharmacist in the similar package in the opaque envelopes with allocated numbers.

The primary outcome was to compare the pain scores during the operation between both groups. The secondary outcome was to evaluate the side effects of the local lidocaine spray. The data was presented as continuous scores (with mean and standard deviation (SD), and/or as dichotomized scores (with number and percentage).

The sample size was calculated using the n4Studies program to compare two independent means[19, 20], based on data from the study by Korsuwan, which evaluated the effectiveness of 10% lidocaine spray for pain relief during office-based endometrial biopsy[11]. We referenced research on endometrial sampling, due to the lack of published data on mean pain scores specific to the MVA procedure. Endometrial biopsy was selected as a reference point because of its procedural similarities to MVA. The calculation used the mean pain score of

the test group (mean 1 = 3.24, SD 1 = 1.58) and the control group (mean 2 = 2.58, SD 2 = 1.79), with a 1:1 ratio between groups. The significance level (alpha) was set at 0.05, and the power (1-beta) at 80%. This resulted in the required sample size of 103 participants per group. Adding 5% for potential dropouts, the total sample size was adjusted to 216 participants.

The baseline characteristics of the participants were compared between lidocaine spray and placebo group using unpaired t test, Chi square test or Fisher's exact test depending on appropriateness. A two-sided p value < 0.05 was considered statistically significant. For the primary and secondary outcomes, the mean difference of pain score between groups with the 95% confidence interval for the continuous outcome and the Pearson chi square or Fisher exact test for the dichotomous outcomes were used. For the main analysis, all outcomes were analyzed using unpaired t-test or logistic regression analysis. All analyses were performed according to the intention-to-treat principle using Stata statistical program version 13.

Results

In the present study, 216 patients were enrolled; 108 patients were randomly assigned to the manual vacuum aspiration with lidocaine spray group, and 108 patients were randomly assigned to the manual vacuum aspiration with placebo group. No patients were excluded by the exclusion criteria. The study details are shown in Fig. 2.

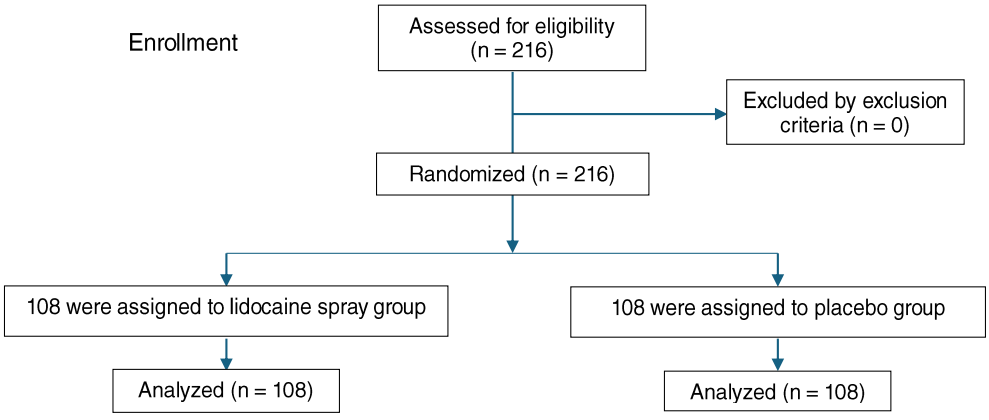

Fig. 2. CONSORT diagram.

The demographic characteristics are present in Table 1. There was no statistically significant difference in age, number of gravid, history of vaginal delivery, history of manual vacuum aspiration, menopausal status, underlying diseases include hypertension, diabetes mellitus, hematologic diseases, and the indications for MVA between groups.

The primary outcome is shown in Table 2. The mean VAS at immediately post MVA in the lidocaine spray was significantly less than the placebo group (1.62 ± 2.10 versus 2.37 ± 2.43 cm; mean difference 0.75; 95% CI (0.13,1.36); p = 0.016). There was no significant difference in pain scores at the time after applying lidocaine spray, during the tenaculum application, during the MVA procedure, and 30 minutes post-MVA between two groups.

The secondary outcome is shown in Table 3. In both MVA groups (lidocaine spray and placebo), dizziness was the most common side effect, followed by with nausea vomiting, unstable vital signs such as hypotension, tachycardia, respectively. However, no statistically significant difference between the two groups was demonstrated.

Table 1. Baseline characteristics of the patients.

Characteristics	MVA with Lidocaine spray group (n = 108)	MVA with placebo group (n = 108)	p value
Age (year), mean ± SD	46.06 ± 10.13	45.72 ± 10.29	0.805*
Gravida, mean ± SD	2.12 ± 1.21	2.14 ± 1.24	0.868*
History of vaginal delivery n (%)	72 (66.67)	80 (74.07)	0.233**
Previous history of MVA n (%)	22 (20.37)	27(25.00)	0.417**
Body mass index (Kg/m^2), mean ± SD	25.03 ± 5.33	25.63 ± 4.86	0.387*
Menopause, n (%)	22 (20.37)	29 (26.85)	0.262**
Underlying diseases			
Hypertension, n (%)	14 (12.96)	15 (13.89)	0.842**
Diabetes mellitus, n (%)	14 (12.96)	12 (11.11)	0.676**
Hematologic diseases, n (%)	2 (1.85)	3 (2.78)	0.651**
Other, n (%)	17 (15.74)	14 (12.96)	0.560**
Indications of MVA			
Abnormal uterine bleeding, n (%)	102 (94.44)	99 (91.67)	0.422**
Pyometra or hematometra, n (%)	6 (5.56)	9 (8.33)	0.422**

SD: standard deviation, MVA: manual vacuum aspiration

* p value was calculated by unpaired t test, ** p value was calculated by Pearson chi square

Table 2. Pain scores during and after Manual Vacuum Aspiration procedure.

	MVA with lidocaine spray group (n = 108)	MVA with placebo group (n = 108)	mean difference (95% CI), p value*
Pain score after apply lidocaine spray, mean ± SD	0.99 ± 1.81	0.86 ± 1.75	0.12 (-0.60 to 0.34),0.593
Pain score after applying tenaculum, mean ± SD	1.98 ± 1.81	2.24 ± 2.45	0.25 (-0.32 to 0.83), 0.379
Pain score during MVA procedure, mean ± SD	3.73 ± 2.68	4.03 ± 2.83	0.30 (-0.43 to 1.04), 0.416
Pain score immediately post MVA procedure, mean ± SD	1.62 ± 2.10	2.37 ± 2.43	0.75 (0.13 to 1.36), 0.016
Pain score post MVA procedure 30 minutes, mean ± SD	0.37 ± 1.02	0.46 ± 0.98	0.09 (-0.17 to 0.36), 0.499

SD: standard deviation, MVA: manual vacuum aspiration, CI: confidence interval

*p value was calculated by unpaired t test

Table 3. Side effects during manual vacuum aspiration.

	MVA with Lidocaine spray group (n = 108)	MVA with placebo group (n = 108)	p value*
Nausea and vomiting, n (%)	3 (2.78)	3 (2.78)	1.000
Dizziness, n (%)	48 (44.44)	45 (41.66)	0.680
Unstable vital signs (hypotension tachycardia), n (%)	2 (1.85)	4 (3.70)	0.408

MVA: manual vacuum aspiration

*p-value was calculated by Pearson chi square

Discussion

In the present study, lidocaine spray significantly decreased the VAS pain score immediately post-MVA compared to the placebo, with a mean difference of 0.75; 95%CI 0.13-1.36. The VAS pain score after applying tenaculum, during MVA and post MVA 30 minutes were not significantly difference between groups.

The reason for the reduction in pain during the immediately post-MVA period can be attributed to lidocaine's mechanism of action. Lidocaine blocks sodium influx through the cell membrane, which blocks nerve impulses passing from the uterovaginal or Frankenhauser's plexus to the sacral spinal nerve 2-4. These nerves supply the upper vagina and cervix and causes pain due to cervical dilatation during MVA[11, 12]. However, while this difference is statistically significant, its clinical significance remains unclear due to the relatively small mean difference.

However, a previous study has shown that the absorption of lidocaine through the cervical mucosa is relatively low and inconsistent, with significant patient-to-patient variation depending on application techniques and mucosal conditions[21]. This limitation may explain that pain score did not reduce during the application of the tenaculum. Moreover, local lidocaine spray has a minimal effect on the uterus, which likely accounts for the lack of difference in pain scores between groups during the MVA procedure. Despite this, lidocaine spray was selected for this study due to its established mechanism of action in blocking nerve impulses from the cervix and its potential to reduce cervical pain during MVA. The choice reflects its hypothesized contribution to a multimodal pain management approach, particularly in addressing pain from cervical manipulation, a significant component of procedural discomfort.

Previous studies have demonstrated significant pain reduction with the use of lidocaine in various gynecological procedures. For example, Korsuwan et al[11] reported the effectiveness of 5 puffs of 10% local lidocaine spray for pain relief during office-based endometrial biopsy. Lidocaine spray significantly reduced pain scores during and immediately after the procedure. Limwatanapan et al[9] compared the effectiveness of lidocaine spray and paracervical block for pain control during loop electrosurgical excision procedures. The study found that lidocaine spray resulted in slightly higher pain scores than paracervical block, but the difference was neither clinically nor statistically significant. However, lidocaine spray had fewer adverse effects. Another study by Arora et al[22] studied pain control during dilatation and curettage and fractional curettage, comparing intrauterine lignocaine with normal saline, both combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and paracervical block. The lignocaine group experienced significantly less pain at all stages compared to the placebo group. Pinya et al[23] compared lidocaine spray combined with intrauterine lidocaine to paracervical block during fractional curettage. Their study reported significantly lower pain scores during the procedure with the combined use of lidocaine spray and intrauterine lidocaine, as opposed to paracervical block alone. The synergistic effect observed with the combination highlights the importance of targeting both cervical and uterine pain.

In contrast, Piyawetchakarn et al[13] examined the effect of lidocaine spray for reducing pain during pipelle endometrial aspiration biopsy in a randomized trial comparing lidocaine spray, placebo, and no intervention. Pain scores at baseline, during biopsy, and post-procedure were not significantly different across the groups. Maneenuch et al[24] investigated the analgesic effect of lidocaine spray during endometrial biopsy and found that while the spray reduced pain scores during cannula insertion compared to a placebo, the differences were not statistically significant. Kotchanipha et al[25] compared the use of lidocaine prilocaine cream and intracervical injection for pain relief during loop electrosurgical excision procedure. Although the cream was less invasive and provided better pain relief during anesthetization, the overall pain scores during the procedure were not significantly different between groups. Our study aligned more closely with the

findings of Piyawetchakarn et al, Maneenuch et al, and Kotchanipha et al, as no statistically significant reduction in pain during the MVA procedure with lidocaine spray was observed. These results collectively highlight the variability in lidocaine's effectiveness across different procedures and underscore the need for further research into its role within multimodal pain management strategies, tailored to specific pain sources and procedural contexts.

Despite results from this study advocating use of lidocaine spray along with intravenous sedation providing some level of pain relief, significant pain reduction was observed only at immediately post-MVA. The results from other time points also indicated that using lidocaine spray tends to reduce pain, but the reduction was not statistically significant. This could be due to various factors, such as the stress, anxiety, or pain awareness is different for each person, during MVA a canular which apply to uterus and tenaculum which apply to cervix may stimulate pain receptors in both the uterus and the cervix, contributing to more pain score. However, the removal of both the cannula and tenaculum immediately post-MVA explains why the pain score during MVA is higher than immediately after the procedure. These data could be useful for future studies aimed at improving pain relief during the MVA procedure.

The clinical implications of this study indicate that while cervical lidocaine spray demonstrated a reduction in pain at a specific time point during the MVA procedure, the overall clinical relevance appears limited, given that the mean pain score difference was less than one. This finding suggests the multimodality pain control in MVA procedure. However, the further studies should include a wider variety of clinical applications and the addition of other drugs to decrease uterine pain[26]. For example, NSAIDs combined with local lidocaine spray could be used as multimodal pain control aimed at reducing opioid dosage and side effects. Further studies could also explore such multimodal strategies, as well as investigate the impact of increasing the lidocaine spray dosage to optimize its effectiveness across multiple stages of the procedure.

The strength of this study lies in its randomized controlled design with an adequate sample size to address the outcome of interest. The double-blinded approach, combined with the use of a placebo in similar packaging, effectively minimizes bias. However, several limitations should be noted. First, the pain scores were based on subjective patient evaluations, which are inherently influenced by individual perception and may lead to variability in pain assessment. Future studies could incorporate objective measures of pain, such as physiological indicators like heart rate or blood pressure alongside patient-reported outcomes. Moreover, the use of validated multi-dimensional pain assessment tools could further reduce variability and enhance the reliability of pain assessments. Secondly, the use of meperidine as an analgesic prior to the procedure could have impacted the pain scores, potentially masking differences in pain levels between the intervention and placebo groups. Additionally, the study did not record the number of aspirations each participant underwent, which may have affected their pain perception, as prior experience with the procedure could influence reported pain levels.

Conclusion

Lidocaine spray has been shown to reduce pain immediately post-MVA without associated serious side effects, suggesting its potential role as an adjunctive analgesic in pain management strategies for the MVA procedure.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

The Effects of Autologous Platelet-rich Plasma Supplement during Sperm Cryopreservation on Post-cryopreserved Sperm Quality

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ABSTRACT

Objectives: This study aimed to evaluate human sperm vitality after cryopreservation by comparing a cryopreservation medium with and without the addition of autologous platelet-rich plasma (aPRP).

Materials and Methods: Semen samples were collected from normozoospermic men. Each sample was separated into two tubes: one without aPRP supplementation and one with 5% aPRP supplementation. Both tubes were cryopreserved for 14 days. Sperm parameters, including sperm concentration, motility, morphology, vitality, and deoxyribonucleic acid (DNA) fragmentation index (DFI), were measured and analyzed.

Results: Fifteen semen samples were included. After cryopreservation, sperm vitality was significantly higher in specimens with aPRP supplementation compared to those without (32.13% ± 12.02% vs 26.07% ± 9.30%, respectively, p = 0.009). There were no significant differences between the two groups in other sperm parameters, including sperm concentration (12.73 x 106/mL (interquartile range (IQR) 21.95 x 106/mL) vs 14.50 x 106/mL (IQR 25.31 x 106/mL), p = 0.053), morphology (4.40% ± standard deviation (SD) 0.98% vs 4.40% ± SD 1.18%, p > 0.999), total motility (8.73% (IQR 9.16%) vs 8.56% (IQR 11.24%), p = 0.410), progressive motility (5.67% (IQR 8.66%) vs 6.61% (IQR 6.35%), p = 0.887), and DFI (12.00% (IQR 15%) vs 17.00% (IQR 26%), p = 0.139).

Conclusion: The supplementation of cryopreservation media with aPRP significantly increased sperm survival rates after the freeze-thaw process. These findings suggest that aPRP may be an effective adjunct in cryopreservation protocols to improve sperm viability. The impact of combined additional high efficiency cryoprotectants on relevant reproductive outcomes, including fertilization, blastocyst formation, and pregnancy rates, needs further investigation.

Keywords: cryopreservation, platelet-rich plasma, semen analysis, sperm, sperm parameter.

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ผลของการแช่แข็งอสุจิแบบผสมส่วนประกอบเกล็ดเลือดเข้มข้นของตนเองต่อคุณภาพของอสุจิหลังละลาย

เฌอมินทร์ ฐิติภัทร์เลิศเดช, นิศานาถ บุญอิ้ง, กัญณภัทร เกสรสุคนธ์, ธัญชนก เจนจิตศิริ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความแตกต่างของอัตราการมีชีวิตของอสุจิที่ผ่านการแช่แข็งแบบปกติ และแช่แข็งแบบผสมส่วนประกอบเกล็ดเลือดเข้มข้น*

วัสดุและวิธีการ: *น้ำเชื้ออสุจิจากอาสาสมัครเข้าร่วมวิจัยที่มีคุณภาพอสุจิปกติ ถูกแบ่งเป็นสองกลุ่ม กลุ่มที่ไม่ผสมส่วนประกอบเกล็ดเลือดเข้มข้น และกลุ่มที่ผสมส่วนประกอบเกล็ดเลือดเข้มข้นร้อยละ 5 จากนั้นทั้งสองกลุ่ม ถูกนำไปเข้าสู่กระบวนการแช่แข็งเป็นระยะเวลา 14 วัน และเมื่อครบระยะเวลากำหนด ทั้งสองกลุ่มจะถูกนำมาวิเคราะห์คุณภาพอสุจิอีกครั้ง รวมถึงวิเคราะห์การแตกหัก deoxyribonucleic acid (DNA) ของอสุจิ (DNA fragmentation index)*

ผลการศึกษา: *อาสาสมัคร 15 คน ถูกนำมาเข้าร่วมกระบวนการวิจัย หลังผ่านกระบวนการแช่แข็ง พบว่า อัตราการมีชีวิตรอดของอสุจิ (sperm vitality) ในกลุ่มที่ผสมส่วนประกอบเกล็ดเลือดเข้มข้น สูงกว่าในกลุ่มกลุ่มที่ไม่ผสมส่วนประกอบเกล็ดเลือดเข้มข้น อย่างมีนัยสำคัญทางสถิติ, 32.13 ± 12.02 และ 26.07 ± 9.30, ตามลำดับ (p=0.009) ทั้งสองกลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญในอัตราความเข้มข้นของอสุจิ (sperm concentration) 12.73 x 106/mL (interquartile range (IQR) 21.95 x 106/mL) และ 14.50 x 106/mL (IQR 25.31 x 106/mL) (p=0.053); รูปร่างของอสุจิ (morphology), 4.40% ± standard deviation (SD) 0.98% และ 4.40% ± SD 1.18% (p>0.999); การเคลื่อนที่ของตัวอสุจิโดยรวม (total motility), 8.73% (IQR 9.16%) และ 8.56% (IQR 11.24%) (p=0.410) และการเคลื่อนที่ของอสุจิที่เคลื่อนที่เป็นเส้นตรงไปข้างหน้า (progressive motility), 5.67% (IQR 8.66%) และ 6.61% (IQR 6.35%) (p=0.887) รวมไปถึงอัตราการแตกหัก DNA ของอสุจิลดลง ในกลุ่มที่ผสมส่วนประกอบเกล็ดเลือดเข้มข้น เมื่อเทียบกับกลุ่มที่ไม่ผสมส่วนประกอบเกล็ดเลือดเข้มข้น 12.00% (IQR 15%) และ 17.00% (IQR 26%) ตามลำดับ (p=0.139).*

สรุป: *การผสมส่วนประกอบเกล็ดเลือดเข้มข้นของตนเอง ช่วยเพิ่มอัตราการมีชีวิตรอดของอสุจิหลังแช่แข็งและละลายอย่างมีนัยสำคัญทางสถิติ จากการศึกษาในวิจัยครั้งนี้ จึงแนะนำว่าการผสมส่วนประกอบเกล็ดเลือดเข้มข้นของตนเองอาจมีประโยชน์ในประบวนการแช่แข็งอสุจิเพื่อเพิ่มอัตราการมีชีวิตรอดหลังละลายแช่แข็ง การศึกษาเกี่ยวกับอัตราการปฏิสนธิ การเจริญเติบโตของตัวอ่อน และอัตราการตั้งครรภ์ยังต้องการการศึกษาต่อไปในอนาคต*

Introduction

Sperm cryopreservation is a procedure used to maintain male reproductive capacity by using several freezing techniques and special sperm freezing media. This ensures the availability of stored sperm for reproductive purposes at a later time, and may be used before cancer treatment[1], before undergoing a vasectomy[2] or other obstructive surgeries[3], in patients with autoimmune disorders or immunosuppressive therapies[4], hematopoietic stem cell disorder and transplantation[2], and even for donor sperm, which needs to be stored for at least 6 months to enable repeat blood testing for human immunodeficiency virus (HIV) before being used for insemination[2, 5]. It may also be used when a man is unable to provide a sufficient volume of semen on the day of egg retrieval in assisted reproductive technologies (ART)[6]. Osmotic alterations, freezing shock, intracellular ice crystal formation, and oxidative and mechanical stressors intrinsic to the freeze-thaw process are the main causes of decreased vitality, motility, and increased deoxyribonucleic acid (DNA) breakage of spermatozoa during semen cryopreservation[7]. The development of freezing procedures, freezing equipment design, vitrification techniques, and sperm freezing media supplementation have been explored to minimize cryoinjury[8]. Previous studies have shown that antioxidants, peptides, fatty acids, blood plasma, nanoscale material elements, biologically active equivalents, and botanical essential oils have significant cryoprotective effects and improve sperm quality following cryopreservation[5].

Platelet-rich plasma (PRP) is a concentrated serum of platelets that has a concentration around seven times higher than the normal platelet concentration. Enriched with growth factors, cell-activating substances, cytokines, cell adhesion molecules (CAMs), and angiogenic factors, this substance enhances the quality of sperm parameters. An example of one of these factors is the hormone insulin-like growth factor-I (IGF-I), which is an important regulator of spermatogenesis and functions as an effective polypeptide that promotes cell division, metabolism, and differentiation. Furthermore, it has been shown that IGF-I and vascular endothelial growth factor (VEGF) enhance sperm motility, vitality, and the structural integrity of mitochondria and plasma membranes after cryopreservation[9, 10]. Moreover, studies have demonstrated that fibroblast growth factor 2 (FGF-2) stimulates the process of phosphorylating fibroblast growth factor receptors (FGFRs), triggering activation of the flagella. This leads to an increase in both total and progressive sperm motility[11]. The superoxide dismutase (SOD) in PRP neutralizes reactive oxygen species (ROS), which induce oxidation of the sperm plasma membrane to protect against cryoinjury[12, 13]. PRP derives its cellular activity and potential therapeutic benefits mostly from its extensive variety of cytokines, various growth factors, and peptide hormones[14, 15].

We assessed the impact of adding an autologous platelet-rich plasma (aPRP) to sperm cryopreservation medium on improving sperm motility and vitality and minimizing DNA fragmentation after vitrification, in comparison to traditional cryopreservation media. In a previous study conducted in China[6], the addition of PRP during sperm cryopreservation significantly promoted sperm motility and viability, while providing minimal protection against excessive formation of ROS and intracellular freezing damage. Furthermore, a study published in Iran[16] found that PRP had an advantageous effect on both sperm motility and survival rates or vitality.

Therefore, we hypothesized that aPRP may act as a cryoprotectant, protecting sperm from damage caused by the freeze-thaw process. This study aimed

to analyze the impact of aPRP supplementation on human sperm by evaluating indicators such as sperm viability, concentration, motility, and DNA fragmentation after the cryopreservation and thawing process.

Materials and Methods

The participants in this study were 20 men, aged between 20 and 40 years old, who were receiving care or were medical staff at Rajavithi Hospital in Bangkok, Thailand and who volunteered to participate. Prior to their participation in the clinical trial, all participants provided informed consent. Once consent was obtained, semen analysis was performed on each sample.

All 20 semen samples were obtained by masturbating into sterile plastic containers after a period of sexual abstinence for 2 to 7 days. The samples were immediately analyzed for sperm parameters within one hour of collection, utilizing a computer-assisted semen analysis (CASA) system according to the 6th edition of the World Health Organization (WHO) guidelines[17].

Samples that did not satisfy the minimal requirements established by the WHO guidelines or had a sperm volume below 2 mL were excluded from this study. Only samples that met the WHO criteria were included, and each semen sample was divided into two specimens, each containing 1 mL each (Fig. 1).

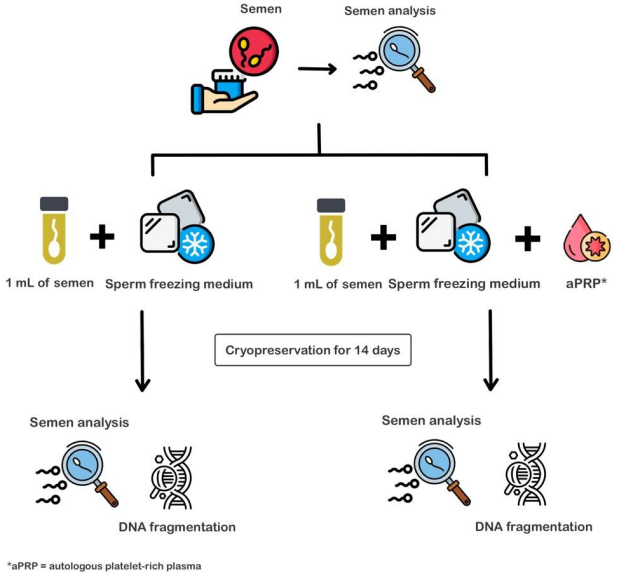

Fig. 1. Study flow diagram shows the methods applied to the control group (left side) and the autologous platelet rich plasma (aPRP) supplementation group (right side).

Assessment of sperm concentration and motility was conducted utilizing a CASA system. Sperm motility was categorized into three distinct groups: progressive motility, characterized by active movement of sperm, either at a fast or slow speed, in a linear or circular motion; non-progressive motility, encompassing all other patterns of active tail movements without any obvious progression; and immotile, indicating the absence of active tail movements. This study considered both progressive motility and total motility, which can be further classified as progressive motility and non-progressive motility, according to the 6th edition of the WHO guidelines[17].

Evaluation of sperm viability was conducted using the eosin-nigrosine staining technique. Equal volumes of 10 µl of each sample were combined with a dye solution including 1% eosin Y and 10%

nigrosine and then rapidly smeared onto a glass slide and allowed to dry spontaneously at room temperature prior to being analyzed using 1,000x light microscopy. Spermatozoa exhibiting red or dark pink heads were classified as non-viable cells, while unstained spermatozoa were considered live or viable[17]. The ratio of dead to living spermatozoa was established by observing a minimum of 200 sperm cells[6].

Spermatozoa are composed of a head and tail. The midpiece refers to the segment of the tail that is linked to the head and includes a thicker section housing mitochondria. The remaining section of the tail comprises the main sperm component, which is an axoneme or ciliary structure encased by thick outer fibers, together with a fibrous covering including longitudinal columns and an endpiece. Given the limited visibility of the endpiece under a light microscope, it is reasonable to regard the cell as consisting of a head (and neck) and tail (midpiece and major piece). In order to classify a spermatozoon as normal, the head, midpiece, tail, and cytoplasmic residue must all be normal. All borderline forms must be regarded as abnormal[17].

To evaluate sperm morphology, ejaculate smears were prepared by air-drying, followed by fixation and staining to enhance the visualization of spermatozoa. In this study, the slides were fixed using a fixative for 15 minutes before undergoing Papanicolaou staining, in accordance with WHO recommendations[17]. Subsequently, the slides were analyzed under 1,000x light microscopy. A minimum of 200 spermatozoa were examined to assess their morphological characteristics and determine the proportion of those with normal forms.

DNA fragmentation was assessed using the sperm chromatin dispersion (SCD) assay kit (HaloSperm®, Halotech, Madrid, Spain). In summary, a small amount of undamaged or post-thaw semen was added to molten agarose, cooled to 37°C, thoroughly mixed, and then set on a Super-Coated Slides (SDS) in the SCD assay kit. In accordance with the manufacturer's instructions, the solidified gel slides were placed in denaturation and lysis solutions, fixed, stained, and examined using bright-field microscopy[18]. Three hundred sperm were randomly selected for each sample and examined using bright-field microscopy with a green filter. The percentage of sperm exhibiting green fluorescence was used as the DNA fragmentation index (DFI), as determined by a CASA system.

Spermatozoa with a substantial or moderately sized halo were deemed normal, suggesting the absence of DNA fragmentation, whereas spermatozoa with a small or no halo were categorized as having fragmented DNA. The DFI was determined by calculating the proportion of spermatozoa with fragmented DNA, encompassing those with a small halo, no halo, and halo-degraded (resulting in fragments) (Fig. 2).

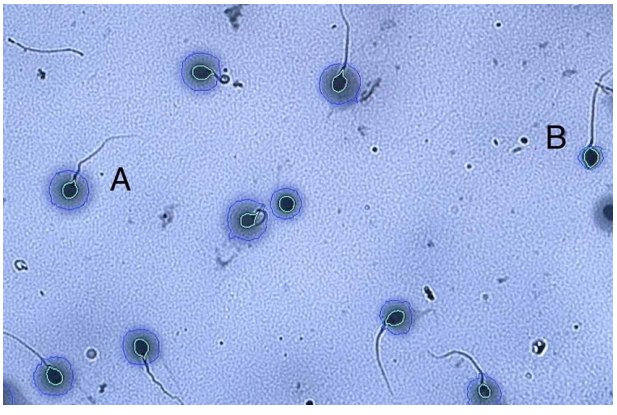

Fig. 2. A: Sperm with a large-sized halo (big halo) means a normal sperm or no deoxyribonucleic acid (DNA) fragmentation, B: Sperm with a small-sized halo (small halo) means a sperm with fragmented DNA, as seen using a computer-assisted semen analysis system.

To prepare aPRP, a blood sample was collected from a donor. The blood was collected into four 3 mL tubes filled with sodium citrate as an anticoagulant solution. After mixing the anticoagulant and blood by inverting the tubes several times, the samples were moved into centrifuge tubes and centrifuged at 1,000 revolutions per minute for 10 minutes.

After centrifugation, the samples had divided into three distinct layers: the supernatant (uppermost layer), the intermediate buffy coat (middle layer), and the red blood cells (bottom layer). Subsequently, the upper layer was discarded, and the middle layer was transferred to another centrifuge tube then centrifuged again at 1,000 revolutions per minute for 10 minutes.

Following the second centrifugation, the sample was roughly divided into three, with the upper two-thirds of the supernatant being discarded. The layer of liquid remaining at the bottom was identified as PRP[19]. Following this, the PRP in the specimen was measured via a cell analyzer; 1×106 platelets per µL were used as autologous aPRP in this study[6, 20].

After completion of the semen analysis, each semen sample was separated into two 1 mL samples: one for aPRP supplementation and the other without, according to the procedure outlined in a previous study[6]. Each specimen was carefully titrated at room temperature with an equivalent volume (v/v; 1:1) of sperm-freezing medium (glycerol, sucrose, and egg yolk-free solution (Origio®)). This was done by adding the medium drop by drop into the semen and carefully mixing the solution after each addition. The mixture requiring aPRP supplementation was supplemented with 5% aPRP and properly mixed. After 10 minutes, the mixtures were transferred into a sterile cryotube and positioned for a 30-minute upward exposure to liquid nitrogen vapor at a height of 3–5 cm above the liquid nitrogen surface. After that, the samples were cryopreserved in liquid nitrogen for 14 days. After 14 days, the samples were thawed at a temperature of 37°C for 10 minutes. Immediately following centrifugation at 2,000 revolutions per minute for 5 minutes, spermatozoa analysis was performed. The supernatant was discarded, and the spermatozoa resuspended with sperm washing medium[16].

Statistical analysis of the data collected in this study was conducted using SPSS software, version 25 (IBM Corp., Armonk, NY, USA). The quantitative findings were reported as the mean ± standard deviation, and median ± interquartile range (IQR) were used to represent the quantitative results for non-normally distributed data. The statistical analyses included the use of the paired student's t test, McNemar test, and Wilcoxon signed-rank test. A p value of less than 0.05 was considered as statistically significant.

Results

Twenty participants were enrolled between August 1, 2023, and August 1, 2024. Two participants were excluded due to abnormal semen analysis, according to the 6th edition of the WHO guidelines[17]. The specimens of 18 participants were divided into two prior to the freeze-thaw process. After 14 days of freezing and thawing, three pairs of specimens had a laboratory error: two of them were not analyzed for sperm motility, and one of them was not analyzed for DNA fragmentation. A total of 15 pairs of specimens were included in the final analysis (Fig. 3). The baseline characteristics of these 15 participants are displayed in Table 1.

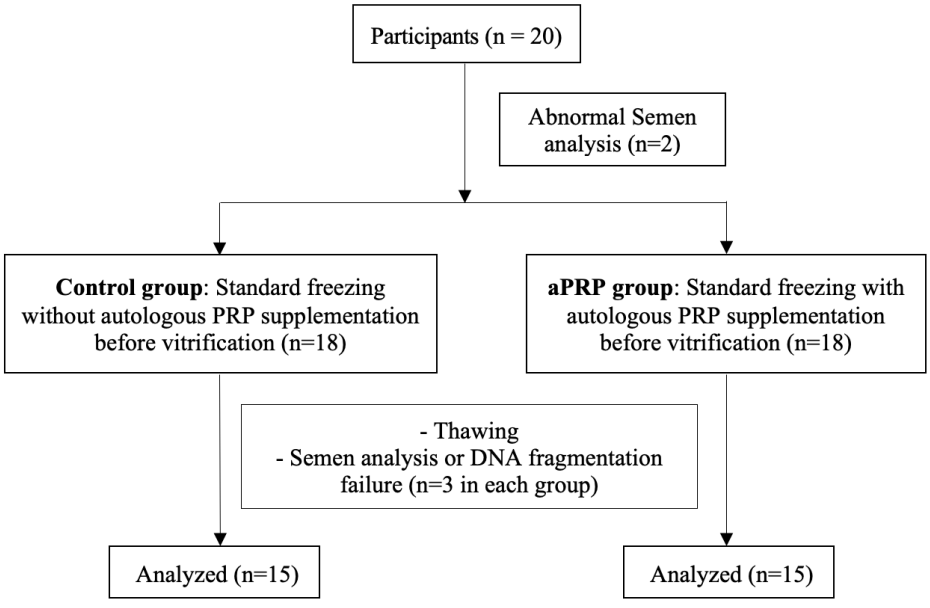

Fig. 3. Consort Flow Diagram.

DNA: deoxyribonucleic acid, aPRP: autologous platelet-rich plasma, PRP: Platelet-rich plasma

Table 1. Baseline characteristics of 15 participants.

Characteristic	
Age (yrs.), mean ± SD	27.3 ± 3.8
BMI (kg/m^2), mean ± SD	23.7 ± 3.5
Education level, n (%)	
Bachelor's degree	14.0 (93.3)
Master's degree or above	1.0 (6.7)
Occupation, n (%)	
Medical staff	6.0 (40.0)
College student	5.0 (33.3)
Other	4.0 (26.7)
Underlying disease, n (%)	
None	11.0 (78.6)
Allergic rhinitis	3.0 (21.4)
Current medication, n (%)	
None	11.0 (73.3)
Yes	4.0 (26.7)
Smoking status, n (%)	
None	14.0 (93.3)
Yes	1.0 (6.7)
Alcohol consumption, n (%)	
None	13.0 (86.7)
Yes	2.0 (13.3)
History of reproductive surgery, n (%)	
Never	15.0 (100.0)

BMI: body mass index, SD: standard deviation

The baseline sperm parameters of these 15 participants before cryopreservation are shown in Table 2. The analysis of the effects of sperm parameters after cryopreservation (freeze–thaw) without and with the addition of aPRP on sperm concentration, motility, morphology and vitality is presented in Table 3.

Table 2. Analysis of baseline sperm parameters for 15 participants prior to cryopreservation.

Semen parameters	Before cryopreservation
Sperm vitality (%), mean ± SD	81.07 ± 13.04
Sperm concentration (x106/mL), median (IQR)	40.46 (40.94)
Motility	
- Total motility (%), median (IQR)	72.49 (37.65)
- Progressive motility (%), median (IQR)	58.87 (35.63)
Normal morphology (%), mean ± SD	4.53 ± 1.30

IQR: interquartile range, SD: standard deviation

Table 3. The effects of cryopreservation on sperm parameters and DNA fragmentation without and with the addition of autologous platelet-rich plasma (aPRP).

Semen parameters	Without aPRP supplementation	With aPRP supplementation	p value
Sperm vitality (%), mean ± SD	26.07 ± 9.30	32.13 ± 12.02	0.009
Sperm concentration (x106/mL), median (IQR)	14.50 (25.31)	12.73 (21.95)	0.053
Motility			
- Total motility (%), median (IQR)	8.73 (9.16)	8.56 (11.24)	0.410
- Progressive motility (%), median (IQR)	5.67 (8.66)	6.61 (6.35)	0.887
Normal morphology (%), mean ± SD	4.40 ± 1.18	4.40 ± 0.98	> 0.999
DNA fragmentation index (%), median (IQR)	17.00 (26.00)	12.00 (15.00)	0.139

IQR: interquartile range, SD: standard deviation, aPRP: autologous platelet-rich plasma

Post-cryopreservation, the viability of sperm was markedly diminished in comparison to the fresh samples in their initial state. Supplementation with aPRP significantly improved the vitality of sperm in comparison to the control group that lacked aPRP (mean difference 6.07, 95% CI 1.81-10.32, p = 0.009). No statistically significant variations were seen in sperm concentration, motility (both total and progressive), or morphology between the two groups.

This study examined the impact of cryopreservation on sperm DNA fragmentation, both with and without the addition of aPRP. The results are presented in Table 3. The experimental group receiving aPRP supplementation had a lower DNA fragmentation index than the control group without aPRP. Nevertheless, there were no statistically significant variations in DNA fragmentation index, regardless of the addition of aPRP (p = 0.139).

Discussion

Sperm cryopreservation is becoming more prevalent for reproductive purposes at a later time, as mentioned earlier. Previous studies have shown that the motility and viability of sperm decrease according to thawing conditions compared to the pre-freeze state[21]. The reduced metabolic rate of spermatozoa during cryopreservation leads to substantial functional and structural alterations due to exposure to cryoprotectants and freeze-thaw processes[21].

The formation of ROS during the cryopreservation process has the capacity to cause oxidative stress and damage the lipid peroxidation of sperm membrane

proteins and DNA[22]. Moreover, the freeze-thaw process can interfere with the glycolysis pathway, leading to a decrease in adenosine triphosphate (ATP) synthesis and thus reducing sperm viability and motility[21, 23]. Oxidative stress is common after freezing; therefore, studies have been conducted in an effort to minimize the production of ROS after the freezing process[24].

Several studies have found that PRP performs effectively in several medical fields including orthopedics, dermatology, stomatology, sports medicine, and reproduction. This is because it is highly safe and effective, uncomplicated to prepare, and does not trigger immunity or other adverse effects[15, 25]. One study revealed that the administration of PRP injections might significantly reduce oxidative stress in the spleen of mice. These advantageous effects can be related to the elimination of the inflammatory, oxidative stress, and anti-apoptotic action of PRP[26]. Nabavinia et al conducted a study using non-autologous frozen PRP and found that the percentage of sperm progressive motility and viability in samples treated with a 1×105/μL concentration of PRP were significantly higher than in the control group[16]. Bo Yan's study used autologous non-frozen PRP to study the effect of several concentrations of PRP on sperm parameters, and found that 5% PRP significantly enhanced sperm motility and viability while also providing protection against oxidative stress and intracellular cryopreservation damage[6]. Buffalo oocytes inseminated with sperm cryofrozen in 5% PRP demonstrated higher fertilization, cleavage and blastocyst rates and lower polyspermy compared to the control. It was concluded that cryofreezing buffalo spermatozoa in autologous PRP-enhanced semen extender increased cryotolerance and fertilizing capability[27]. Therefore, 5% of non-frozen aPRP was used in the current study.

This study found that 5% aPRP supplementation significantly increased sperm vitality post-cryopreservation, consistent with findings from previous studies[6, 16]. However, previous studies found that it not only increased sperm vitality, but also significantly increased sperm progressive motility. There was no statistically significant difference between samples with and without aPRP supplementation in terms of sperm concentration, morphology, total motility, or progressive motility in this study.

Some studies have found that PRP may induce head-to-head sperm agglutination[28]. In this study, we found that head-to-head sperm agglutination increased after thawing, with the majority of agglutination occurring near the slide's border, which may have led to inaccuracies in the CASA system. This may be the reason for the decreasing sperm concentration. Head-to-head motility, shown as sperm agglutination, may lead to failure to detect motility in the CASA system. If sperm motility is inadequate, the vitality test is important in order to distinguish between immotile dead sperm and immotile living sperm[17]. The Bo Yan study showed that the addition of a coagulant to activated aPRP had no impact on sperm agglutination[6]. In our study, we noticed an elevated rate of sperm agglutination, possibly because aPRP was not activated before its administration.

During this study, the sperm morphology after thawing of both aPRP-treated and untreated samples was similar to the morphology prior to freezing, indicating that the aPRP and cryopreservation processes did not damage sperm morphology.

The limitations of this study included the relatively small sample size, which was calculated using the two-dependent-means method, as referenced in Bo Yan's study[6] Similarly, prior studies have also utilized small sample sizes. Another limitation lied in the methodology for preparing aPRP before freezing and aPRP activation as discussed previously, the sperm-washing techniques, and the process of centrifugation after thawing, which may have resulted in a decrease in the concentration of sperm, resulting in inaccurate analysis. The further development of methods to reduce sperm agglutination and other combined additional high efficiency cryoprotectants may prove advantageous in the future. Moreover, a well-designed randomized controlled trial

would enhance the reliability of the findings. Finally, the fertilization rate, rate of blastocyst formation, and pregnancy rate also need further investigation.

Conclusion

Supplementation with aPRP in a standard sperm cryopreservation protocol had a significant positive effect on increasing sperm survival rates and sperm vitality. There were no adverse effects on other sperm parameters, including sperm concentration, motility, or morphology.

Potential conflicts of interest

The authors declare no conflicts of interest.

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The Survival after Surgery of Clinically Early-stage Cervical Cancer in Chonburi Hospital and Multivariable Analysis of Prognostic Factors Influencing Survival

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ABSTRACT

Objectives: To evaluate 5-year overall survival (OS), 5-year disease-free survival (DFS), recurrent rate and identified prognostic clinicopathological factors of patients with clinically early-stage cervical cancer treated with primary surgery in Chonburi Hospital.

Materials and Methods: The medical records of early-stage cervical cancer patients undergoing surgery treatment from January 2012 to September 2023 were reviewed. OS and DFS were obtained. Patients' age, stage, tumor size, histologic type, depth, degree of stromal invasion, lympho-vascular space invasion (LVSI), surgical margin, pelvic node status, and adjuvant treatment were assessed for correlation with DFS.

Results: Three hundred and twelve patients were included. The mean age was 46.8 ± 11.6 years, and the median follow-up was 67.0 months. Fifty-three patients (17.2%) developed recurrent disease. The 5-year OS was 100%, 93.9%, 88.5%, and 81.8% (p = 0.001) according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA, IB1, IB2, and IB3, respectively. The 5-year DFS was 100%, 95.1%, 87.5%, and 74.5%, correspondingly (p = 0.001). The discordance between clinical and surgical upstaging was 13.8% according to FIGO 2018 criteria. In multivariate analysis, stage beyond IB3, tumor size over 4 cm, LVSI, and deep stromal invasion were significant prognostic variables. In contrast, adjuvant postoperative radiotherapy (PORT) in the intermediate and high-risk groups was the protective factor for DFS with a hazard ratio of 0.39 [0.20 – 0.76, p = 0.006].

Conclusion: The 5-year OS and DFS of clinically early-stage cervical cancer were 85.3% and 84.0%, respectively. PORT was the protective factor for recurrence.

Keywords: cervical cancer, survival, surgery, radical hysterectomy, recurrence.

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อัตราการรอดชีวิตหลังการผ่าตัดในผู้ป่วยมะเร็งปากมดลูกระยะเริ่มต้นในโรงพยาบาลชลบุรี และการวิเคราะห์แบบพหุปัจจัยถึงตัวแปรที่มีผลต่อการพยากรณ์โรค

สุวภรณ์ ถินสถิตย์, ทศพล เจียมตน

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราการรอดชีวิตโดยรวมที่ 5 ปี อัตราการปลอดโรคที่ 5 ปี อัตราการกลับเป็นซ้ำ และศึกษาปัจจัยทางคลินิกและพยาธิวิทยาที่มีผลต่อการพยากรณ์โรคในผู้ป่วยมะเร็งปากมดลูกระยะเริ่มแรกที่รับการรักษาแรกด้วยการผ่าตัดในโรงพยาบาลชลบุรี*

วัสดุและวิธีการ: *ทะเบียนผ่าตัดและเวชระเบียนของสตรีที่ถูกวินิจฉัยเป็นมะเร็งปากมดลูกระยะเริ่มต้นและได้รับการรักษาแรกด้วยการผ่าตัดระหว่าง มกราคม 2555 - กันยายน 2566 จะถูกนำมาทบทวนและคำนวณอัตราการรอดชีวิตโดยรวมและอัตราการปลอดโรคปัจจัยทางคลินิกและพยาธิวิทยา ได้แก่ อายุ ระยะ ขนาดมะเร็ง ชนิดซองเซลล์ ความลึก และระดับการลุกลามเข้าเนื้อเยื่อเกี่ยวพัน การลุกลามเข้าหลอดเลือดหรือหลอดน้ำเหลือง การพบมะเร็งที่ขอบชิ้นเนื้อ การกระจายที่ต่อมน้ำเหลืองอุ้งเชิงกราน และการได้รับรังสีรักษาเสริมหลังผ่าตัด จะถูกนำมาวิเคราะห์ความสัมพันธ์กับอัตราการปลอดโรค*

ผลการศึกษา: *จากผู้ป่วยมะเร็งปากมดลูก 312 ราย อายุเฉลี่ย 46.8 ± 11.6 ปี ค่ามัธยฐานการตรวจติดตามคือ 67 เดือน พบมะเร็งกลับเป็นซ้ำ 53 ราย คิดเป็นร้อยละ 17.2 อัตราการรอดชีวิตโดยรวมที่ 5 ปี คือ ร้อยละ 100, 93.9, 88.5, 81.8 (p = 0.001) ของระยะ IA, IB1, IB2 และ IB3 ตาม International Federation of Gynecology and Obstetrics (FIGO) 2018 ตามลำดับ อัตราการรอดชีวิตโดยปลอดโรคที่ 5 ปี คือ 100%, 95.1%, 87.5% และ 74.5% (p = 0.001) ตามลำดับ โดยพบระยะมะเร็งหลังผ่าตัดเพิ่มขึ้นจากระยะทางคลินิค ร้อยละ 13.8 ตามเกณฑ์ของ FIGO 2018 จากการวิเคราะห์พหุตัวแปรพบว่าระยะของมะเร็งมากกว่า IB3, ขนาดมะเร็งมากกว่า 4 เซนติเมตร การลุกลามเข้าหลอดเลือดหรือหลอดน้ำเหลือง และการลุกลามเข้าเนื้อเยื่อเกี่ยวพันชั้นลึก มีผลลดอัตราการปลอดโรค ในทางกลับกันการได้รับรังสีรักษาเสริมหลังผ่าตัดในกลุ่มความเสี่ยงปานกลางและความเสี่ยงสูง เป็นปัจจัยเพิ่มอัตราการปลอดโรค (Hazard ratio of 0.39, 0.20 – 0.76, p = 0.006)*

สรุป: *อัตราการรอดชีวิตโดยรวมที่ 5 ปี และอัตราการปลอดโรคที่ 5 ปี ร้อยละ 85.3 และร้อยละ 84.0 ตามลำดับ การได้รับรังสีรักษาเสริมหลังผ่าตัดเป็นปัจจัยลดการกลับเป็นซ้ำ*

คำสำคัญ: *มะเร็งปากมดลูก, อัตราการรอดชีวิต, อัตราการปลอดโรค, การผ่าตัด, การกลับเป็นซ้ำของมะเร็ง*

Introduction

Cervical cancer ranks as the most prevalent malignancy among all gynecological cancers in Thailand, serving as the primary cause of mortality for up to 342,000 individuals out of 604,000 women diagnosed with cervical cancer in 2020[1]. According to the 2021 cancer registry, Chonburi province ranks third in terms of the number of newly diagnosed cancer patients, trailing behind Bangkok and Chiang Mai provinces[2]. Chonburi Hospital, a longstanding tertiary care facility, accommodates a substantial caseload of cervical cancer patients, approximately ranging from 100 to 200 cases annually. Patients diagnosed at an early stage typically undergo surgical intervention as the primary treatment modality[3]. In cases where there exists a risk of disease recurrence, patients are referred for adjunctive therapy, including radiation or concurrent chemoradiotherapy, at the neighboring Chonburi Cancer Hospital. The hospital actively engages in collaborative research endeavors focusing on locally advanced-stage patients and maintains continuous surveillance of patients' post-treatment.

Internationally, numerous studies have examined survival rates post-treatment across various stages of cervical cancer, comparing the efficacy of different treatment modalities[3-5]. A study conducted in 2008 in the United States evaluated stage IA1–IB patients who underwent radical surgery or radiation therapy, reporting 5-year survival rates ranging from 87% to 92%[4].

In Thailand, studies conducted in many regions display an average 5-year overall survival rate of early-stage cervical cancer range of 62.3 to more than 90.0%[6-10]. Notably, some studies identified clinicopathological factors influencing survival rates, such as histology subtype, tumor size, lymphovascular space invasion (LVSI), and deep stromal invasion, but remain controversial[6-10]. Some studies showed the variables associated with the parametrial invasion that could surgically upstage cervical cancer that underwent radical hysterectomy were deep stromal invasion and pelvic lymph node metastasis, but lack of survival outcomes[11, 12].

Despite the wealth of international research, there remains a dearth of comprehensive data regarding survival rates, disease-free rates, recurrence rates, and the clinicopathological factors influencing outcomes specific to Chonburi province or the Eastern region of Thailand. Such information is crucial for monitoring treatment effectiveness, identifying variations in care, improving the patient supervision process and guiding resource allocation policy in our region.

Materials and Methods

This study represented a single-center, retrospective descriptive study conducted at Chonburi Hospital, Thailand. Ethics approval was granted by the Institutional Review Board of the Chonburi Hospital Medical Education Center under a waiver of informed consent (ref. 2966RH3). The study included all clinically early-stage cervical cancer patients who had been diagnosed preoperatively by punch biopsy or excisional procedure and clinical examination and underwent hysterectomy between January 1, 2012, and September 30, 2023.

In our hospital, all patients were clinically staged as recommended by the International Federation of Gynecology and Obstetrics (FIGO); tumor size was determined solely by the attending gynecologic oncologist during a pelvic examination or colposcopy preceding surgery. However, a minority of our patients could have preoperative imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) because of the long waiting period in our nonprofit, civil hospital setting. The patient must be aimed for primary hysterectomy or radical hysterectomy with pelvic lymphadenectomy (RHND). Patients whose

hysterectomies were abandoned, received neoadjuvant chemotherapy or preoperative irradiation, or with second primary cancer were excluded. The type of hysterectomy depended on the surgeon's decision based on FIGO recommendation. All hysterectomy underwent here was done via laparotomy. Generally, the criteria for referral for postoperative concurrent chemoradiation included pelvic node metastasis, parametrial invasion and/or surgical margin involvement in the high-risk group (Peter criteria)[13], and adjuvant radiation in the intermediated-risk group according to Sedlis criteria[14]. The radiotherapy took place in Chonburi Cancer Hospital with the cooperation of radiologic oncologists.

After completion of treatment, all patients returned to surveillance by history taking and clinical examination every 3-4 months during the first and second year, then every 6 months until the fifth year, and annually thereafter. The vaginal stump cytology was performed at least once a year. Recurrence was defined either by pathological proof or imaging. Disease-free survival (DFS) was calculated as the duration from the day of surgical treatment to the first time of tumor recurrence or death. All deaths were registered by the hospital database and the Cancer Registry Unit of Chonburi Hospital. All patients' statuses were rechecked using the hospital's National Health Security Office (NHSO) unit and the Department of Provincial Administration, Minister of Interior, using the death certificate database. OS was defined as the duration from the surgery until death, regardless of the causes of mortality. Cause of death was extracted by reviewing medical records if expired in the hospital or as defined in the death certificate by physician and authority staff if died outside the hospital. In the case of patients who lost to follow-up, DFS and OS data were censored at the time of patients known to be still alive since the last visit. All alive patients were confirmed directly by calling; survival data were right censored on September 30, 2023.

All pertinent clinical data were obtained and retrospectively reviewed from the medical records include birthdate, comorbidity, body weight, height, type of hysterectomy and associated procedures. Pathological factors include cell type, tumor size, depth, degree of stromal invasion, LVSI, number of pelvic lymph nodes exhibiting metastasis, surgical margin, parametrial and lower uterine segment invasion. Patients diagnosed before 2021 were re-stage according to FIGO's revised criteria 2018 (2021 update). Exclusion was also applied to individuals with incomplete medical record information.

The authors aimed to evaluate the 5-year OS and DFS of all early-staged cervical cancer cases meeting eligible criteria during the study period as the primary objective. Sample size calculation was based on the formula for two sample comparisons of the survival proportion using 1-tail alpha equal 0.05 and power 90%. OS of squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the cervix from the prior study was used for calculation[15]. At least 113 participants per group were needed.

Statistical analysis was undertaken using STATA 14 (StataCorp, College Station, TX). Continuous data were presented as mean (standard deviations) or median (interquartile range, IQR), contingent on the normality of each distribution, while categorical data were delineated using counts and percentages. The Kaplan-Meier method

determined overall survival and disease-free survival at 5 years. Potential clinicopathological factors associated with DFS were compared using the log-rank test. The Cox proportional hazard regression model assessed the risk of recurrent disease or DFS. Univariate and multivariable analysis using significance for all statistical tests was set at a p value < 0.05.

Results

During the study period, three hundred and thirty-nine patients were diagnosed with early-stage cervical cancer and scheduled for simple hysterectomy or radical hysterectomy. Seventeen hysterectomies were abandoned due to gross intraoperative parametrial invasions, gross lymph node metastasis, or positive extra-cervical metastatic evidence on the frozen section. A total of 312 cases were eligible for analysis. The median follow-up time was 67.0 months (IQR 23.1, 111.5 months). The average age was 46.8 ± 11.6 years, with a mean body mass index (BMI) of 24.5 ± 4.8 kg/m^2. The majority of cases (97.4%) were of Thai ethnicity, totaling 304 cases. Fifteen patients (4.8%) were immunocompromised, and 46 (14.7%) were associated with cardiovascular disease or metabolic syndrome. Preoperative imaging (computerized tomography (CT) or magnetic resonance imaging (MRI)) was performed in 58 cases (18.59%) and within normal limits. According to the FIGO's revised criteria 2018 (2021 update), the number of cases was classified as following stages: IA1 = 32 (10.3%), IA2 = 4 (1.3%), IB1 = 82 (26.3%), IB2 = 96 (30.8%), IB3 = 55 (17.6%), and stage higher than IB3 = 43 (13.8%). The majority of cases were squamous cell carcinoma 181 (58.0%), followed by adenocarcinoma 114 (36.5%), and other cell types 17 (5.4%). The type of surgery included radical hysterectomy in 88.5% of cases, modified radical hysterectomy in 7.1%, and simple hysterectomy in 4.5%. Pelvic lymph nodes were removed in 94.9%, with a median of 20 nodes removed per patient. Pathology results showed lesions larger than 4 cm in 74 (23.7%), 122 (35.9%) had deep invasion into the stroma, and 129 (46.7%) had lymphovascular space invasion, which met the criteria for moderate risk of recurrence according to Sedlis criteria of 97 cases (31%). The cancer had spread to pelvic lymph nodes in 28 (10.1%) cases, to the parametrium in 22 (8.0%) cases, and the presence of cancer cells at the surgical margin in 25 (8.0%). According to Peter's criteria, they were classified as high risk of recurrence in 48 (15.4%) cases. Therefore, 145 patients needed adjuvant radiotherapy after surgery, but only 119 received adjuvant treatment. postoperative radiotherapy (PORT) was exclusively in 42 (15.2%) cases and concurrent with platinum in 73 (26.4%) cases. Those who did not receive adjuvant treatment, including those who had pelvic irradiation < 25.0 Gy (incomplete treatment), refused treatment, and those who had poor performance status totaled 29 (9.3%) cases. Discordance between clinical and surgical staging was 43 (13.8%). Overall death was 59 (18.9%), with 46 deaths within 5 years. Due to the overall survival rate of more than half, the expected median survival time estimated using Kaplan-Meier was 119.5 months (95%CI 113.6-125.5). The recurrence rate was 17.0%, with 50 cases recurring within 5 years since hysterectomy. The rate of loss to follow-up more than 2 years was 9.3%. The data was demonstrated in Table 1.

Table 1. Demographic data and clinicopathological characteristics.

	mean	SD
Age (years)	46.8	± 11.6
BMI (kg/m^2)	24.5	± 4.8
	n	**Percent**
Race		
Thai	304	97.4%
Other Southeast Asians	8	2.6%
Underlying disease		
Immunocompromised	15	4.8%
Cardiovascular or metabolic syndrome	46	14.7%
Stage (revised FIGO 2018)		
IA1	32	10.3%
IA2	4	1.3%
IB1	82	26.3%
IB2	96	30.8%
IB3	55	17.6%
Above IB3	43	13.8%
Cell type		
Squamous cell carcinoma	181	58.0%
Adenocarcinoma	114	36.5%
Neuroendocrine carcinoma	14	4.5%
Others	3	0.9%
Procedure		
Radical hysterectomy	276	88.5%
Modified radical hysterectomy	22	7.1%
Simple hysterectomy	14	4.5%
Pelvic lymphadenectomy	296	94.9%
Para-aortic lymphadenectomy	4	1.3%
Median number of pelvic lymph nodes retrieved (IQR)	20	(15-26)
Postoperative adjuvant treatment modality		
No indication for adjuvant treatment	166	53.2%
Adjuvant radiotherapy	42	15.2%
Concurrent chemoradiotherapy	73	26.4%
Adjuvant chemotherapy (without radiotherapy)	4	1.3%
Incomplete or denial of adjuvant treatment	24	7.7%
Omission based on the radiotherapist's opinion and the patient's performance status	5	1.6%
Adverse prognostic factor (not including the micro-invasive stage) (n = 276)		
Presence of LVSI	129	46.7%
Large tumor size (> 4 cm)	74	23.7%
Deep stromal invasion	112	35.9%
Parametrial invasion	22	8.0%
Lymph node metastasis	28	10.1%
Categorized into intermediate risk group (Sedlis criteria)	97	31.0%
Categorized into high-risk group (Peter criteria)	48	15.4%
Discordance between clinical and surgical staging	43	13.8%
Median follow-up time (months, IQR)	67.0	(23.1, 111.5)
Expected median survival time (months, 95%CI)	119.5	(113.6-125.5)
Rate of lost surveillance > 2 year	29	9.3%
Overall recurrence	53	17.0%

SD: standard deviation, BMI: body mass index, SEA: Southeast Asians, FIGO: Federation of Gynecology and Obstetrics, IQR: interquartile range, LVSI: lymphovascular space invasion, CI: confidence interval

Overall survival and disease-free survival

During the study period, the overall survival rate for all stages of cervical cancer was found to be 85.3%. The 5-year OS for patients with early-stage cervical cancer treated with surgery at Chonburi Hospital were as follows: IA1 100%, IA2 100%, IB1 93.9%, IB2 88.5%, IB3 81.8%, and higher than IB3 53.5%. The average 5-year overall survival rate was 86.2 %. When considering specific causes of death from cervical cancer, 5-yr cancer-specific survival were as follows: IA1 100%, IA2 100%, IB1 96.3%, IB2 91.7%, IB3 81.8%, and higher stage IB3 55.8%. The 5-year cancer-specific survival rate from all stages of our study was 87.2%.

Among the 312 patients, 53 (17%) experienced a recurrence of cervical cancer. Half of these recurred in the first two years (media 17.4 months (IQR 9.5-12.1)). Recurrence was confirmed by biopsy or fine needle aspiration or imaging. Five-year disease-free survival rates were 100% for stages IA1 and IA2. However, stages IB1, IB2, IB3, and those higher than IB3 had recurrence rates of 4.9%, 12.5%, 25.5%, and 48.8%, respectively. The proportion of survival was plotted in Fig. 1. and 2.

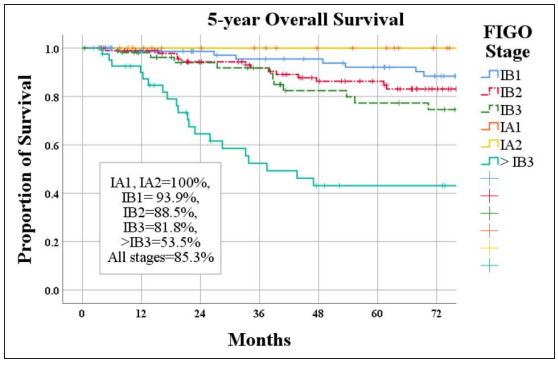

Fig. 1. 5-year overall survival in Kaplan-Meier curve, according to International Federation of Gynecology and Obstetrics 2018 stage.

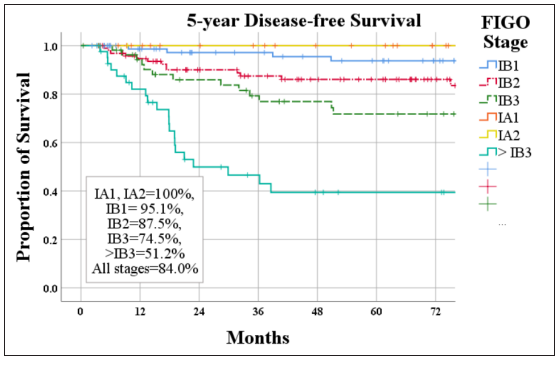

Fig. 2. 5-year disease-free survival in Kaplan-Meier curve, according to 5-year overall survival in Kaplan-Meier curve, according to International Federation of Gynecology and Obstetrics 2018 stage 2018 stage.

Potential clinicopathological prognostic factors

The research data were analyzed to identify factors affecting 5-year DFS using the log-rank test and then Cox proportional hazard models. Significant factors reducing DFS were determined to be as follows: higher stages of cervical cancer had the greatest effect on lowering survival rates compared to stage IB1 (HR 15.46%, 95% CI 5.29-45.23), tumor

size larger than 4 centimeters (HR 7.79, 95% CI 2.69-22.54), deep stromal invasion (HR 10.84, 95% CI 3.34-35.20), presence of LVSI (HR 6.42, 95% CI 3.01-13.67), depth of invasion more than 10 millimeters, parametrial involvement, lower uterus segment invasion, unfree surgical margin, positive pelvic lymph node metastasis and those receiving adjuvant PORT. Notably, age and comorbidities did not significantly affect the survival rate. These findings are summarized in Tables 2 and 3.

Table 2. Univariate analysis of 5-year disease-free survival according to potential clinicopathological factors using log-rank test.

Clinicopathological factor	n	5-year disease-free survival	p value*
Age (years)			0.118
≤ 45	147	81.0%	
> 45	165	86.7%	
Underlying disease			0.219
No	251	84.9%	0.
Immunocompromised	15	66.7%	
Cardiovascular or metabolic syndrome	46	84.8%	
Histology			0.043
Squamous	181	89.0%	
Adenocarcinoma	114	78.1%	
Neuroendocrine	14	64.3%	
Tumor size (cm)			< 0.001
≤ 2	124	96.8%	
> 2	188	75.5%	
Depth of invasion (mm)			< 0.001
≤ 10	199	91.5%	
> 10	113	70.8%	
Degree of stromal invasion			< 0.001
Superficial 1/3	130	97.7%	
Middle 1/3	70	84.3%	
Deep 1/3	112	67.9%	
Lymphovascular space invasion			< 0.001
Absence	183	95.6%	
Presence	129	67.4%	
Lower uterine segment invasion			0.001
Absence	276	86.8%	
Presence	40	65.0%	
Surgical margin involvement			< 0.001
No	287	87.1%	
Yes	25	48.0%	
Parametrial invasion			< 0.001
No	290	86.6%	
Yes	22	50.0%	
Pelvic node metastasis (lymphadenectomy, n = 295)			< 0.001
Absence	267	86.9%	
Presence	28	46.4%	
Adjuvant postoperative radiotherapy or chemoradiotherapy (stage IB and above, n = 279)			0.025
No	164	86.6%	
Yes	115	75.7%	

* log-rank testl

Table 3. Univariate analysis of 5-year disease-free survival according to prognostic clinicopathological factors using Cox proportional hazard models in surgical stage IB1 and above.

Clinicopathological factor	Hazard ratio*	95% confidence interval	p value*
Stage (revised FIGO 2018)			0.004
IB1	1		
IB2	2.56	0.83-7.94	
IB3	5.14	1.68-15.78	
> IB3	15.46	5.29-45.23	
Histological cell type			0.034
Squamous	1		
Adenocarcinoma	1.89	1.05-3.40	
Neuroendocrine	2.79	1.05-7.43	
Tumor size (cm)			0.004
≤ 2	1		
> 2 to ≤ 4	4.73	1.64-13.69	
> 4	7.79	2.69-22.54	
Depth of invasion (mm)			< 0.001
≤ 10	1		
> 10	3.06	1.70-5.50	
Degree of stromal invasion			0.017
Superficial 1/3	1		
Middle 1/3	4.70	1.31-16.86	
Deep 1/3	10.84	3.34-35.20	
Lymphovascular space invasion			< 0.001
Absence	1		
Presence	6.42	3.01-13.67	
Lower uterine segment invasion			0.005
Absence	1		
Presence	2.42	1.31-4.50	
Surgical margin involvement			< 0.001
No	1		
Yes	5.57	2.94-10.56	
Parametrial invasion			< 0.001
No	1		
Yes	4.25	2.18-8.32	
Pelvic node metastasis			< 0.001
Absence	1		
Presence	5.80	3.15-10.68	
Adjuvant postoperative radiotherapy or chemoradiotherapy			0.031
No	1		
Yes	1.85	1.06-3.24	

* Cox proportional hazards regression analysis

In multivariate analysis, only surgically stage > IB3, tumor size larger than 4 centimeters, and deep stromal invasion remained statistically significant, contributing to a decreased 5-year DFS rate. However, adjuvant treatment, either radiotherapy or concurrent chemotherapy, increased the DFS rate after surgery. This data is demonstrated in Table 4.

Table 4. Multivariate analysis of 5-year disease-free survival according to prognostic clinicopathological factors using Cox proportional hazard models.

Variable	Hazard ratio*	95% confidence interval	p value*
Stage > IB3	9.53	2.96-16.07	< 0.001
Tumor size > 4 cm	4.73	2.57-8.71	< 0.001
Deep 1/3 stromal invasion	4.73	1.09-20.62	0.038
Lymphovascular space invasion presence	3.91	1.61-10.25	0.004
Adjuvant postoperative radiotherapy or chemoradiotherapy	0.39	0.20-0.76	0.006

* Cox proportional hazards regression analysis

Discussion

Our study, in a single institute with over 300 patients over 12 years, showed that patients with clinically diagnosed early-stage cervical cancer who were primarily treated with radical hysterectomy and pelvic lymphadenectomy had good survival outcomes with a 5-year OS and DFS of 85.3% and 84.0%. Our OS was similar and consistent with global results of early-stage cervical cancer stratified into stage IA1–IB3 according to the revised FIGO 2018 staging criteria. These studies have reported 5-year OS ranging from 95.8%, 95.0%, 91.6%, 83.3%, and 76.1% in stages IA1 to IB3, respectively[3, 16]. In Thailand, the largest series of patients with stages IA-IIA (FIGO 2009) from Chiang Mai (Suprasert et al 2010)[10] impressively revealed an excellent 10-year disease-free survival of 90% with a 4-fold sample size greater than ours. Despite the relatively higher pelvic node metastasis, parametrial invasion, and vaginal margin involvement than our cohort, the 10-year DFS was better. A total of 66.5% of patients in this study underwent RHND without adjuvant treatment, whereas 12.1% received neoadjuvant chemotherapy. It might reflect the well-experienced clinical-surgical characteristics of the leading institute and the properly selected case. However, the difference in FIGO staging criteria and survival time frame might not ensure comparability. Another study from Songkhla (Chandeying et al 2017)[9] also revealed the 5-year DFS rate of stage IA2-IB1 (FIGO 2009) of AC at 89.3% (95%CI 83.2–93.2), SCC 88.7% (95%CI 84.8 - 91.7) which was similar to our DFS of stage IA2-IB2 (FIGO 2018). Almost all prior studies in Thailand usually used FIGO 2009 criteria, except one recent study from Bangkok (Bangsomboon et al 2022)[8] displayed the 5-year progression-free survival (PFS) of stage IB1, IB2, and IB3 were 83.3%, 90.0%, and 84.2%, respectively. The 5-year OS were 71.4%, 92.2%, and 62.5%, consecutively. The PFS and OS were not different among the 3 sub-stages of IB, which was inconsistent with ours. This disparity may result from the difference in sample size and baseline characteristics, especially the rate of surgically upstaging (35.8%, n = 81) compared to 13.8% (n = 43) of our cohort. Discordance in clinical and surgical staging of cervical cancer can affect survival rates, patients who are pathologically upstaged have a higher risk of recurrence and death[17]. This is because tumor size is a major factor in determining the best treatment planning and survival outcomes. The preferred treatment for tumors smaller than 4 cm is surgery, while primary chemoradiation is recommended for larger tumors. Finally, our results support the novel FIGO 2018 staging criteria in terms of survival and can be used to stratify both OS and DFS.

Our study's clinicopathological factors significantly associated with recurrence and DFS were FIGO 2018 stage > IB3, large tumor size, deep stromal invasion, and presence of LVSI. These variables were well-documented and consistented with global findings. Actually, our "stage > IB3" variable can resemble the presence of any Peter criteria that are generally used to categorize patients into high-risk groups for recurrence[13]. The other three significant factors, tumor size, deep stromal

invasion (DSI), and presence of LVSI, were also in the Sedlis criteria used to divide patients into intermediate-risk groups for recurrence[14]. Hence, this study reassures the clinical application of these two criteria. Postoperative radiotherapy, whether with or without concurrent chemotherapy (CCRT), usually reduced the recurrent rate in early-stage cervical cancer with large tumor size, LVSI, and DSI from 88% (pelvic radiation) versus 79% (no adjuvant treatment) or from 80% (CCRT) versus 63% (PORT) [13, 14]. Our study supports the adjuvant PORT helps improve disease-free survival with a hazard ratio of 0.39 (95%CI 0.20-0.76, p = 0.006). However, a recent study demonstrated that histology-specific nomograms can more accurately and linearly predict the risk of recurrence for both SCC and AC tumors, offering a more contemporary and tailored tool to determine adjuvant treatment[18]. Furthermore, a novel study found that among patients meeting one or two Sedlis criteria, there were no statistically significant differences in OS between those receiving PORT and those without adjuvant treatment, likely due to the increasingly accurate selection of cervical cancer patients eligible for surgery[19].

A strength of our study lied in the long follow-up duration on patients with early-stage cervical cancer surgically treated and monitored at Chonburi Hospital with a median surveillance time of 67.0 months (IQR 23.1-111.5). Second, the lost contact rate for over 2 years was low (9.3%) as we are the only hospital capable of radical hysterectomy in the city, and our cancer manager team and outpatient nurses were willing to reach out to patients when there was a disconnection. Third, our patients diagnosed before 2021 were re-stage according to FIGO's revised criteria 2018 (2021 update); therefore, our stage is current to the international agreement. Fourth, excluding patients with incomplete records may introduce selection bias; however, our hospital transitioned from hard-copy to electronic-based documentation in 2012, ensuring the validity and reliability of the available information. Fifth, the rate of pelvic lymphadenectomy concurrent with radical hysterectomy in our institute was high: 99.3% (296 from 298 type II and type III hysterectomies). Median number of pelvic lymph nodes retrieved (IQR) was 20 (15-26). Therefore, we can ensure the absence of microscopic nodal metastasis.

A limitation of the study was that a minority of our patients could have preoperative imaging such as CT or MRI because of the long waiting period in our nonprofit, civil hospital setting. Many studies recommend utilizing CT/MRI scans to determine the stage before treatment accurately[16, 20] Preoperative imaging can crucially help determine if a patient truly needs a radical hysterectomy or not. In our previous resource-constrained setting, it might have been difficult to assess the spread of the disease, which could have led to an incorrect treatment plan. This lack results in discordance between clinical and surgical staging. Second, due to Chonburi Hospital's inability to perform radiation therapy, we had to rely on treatment information from Chonburi Cancer Hospital as well. Third, we hardly performed paraaortic lymphadenectomy as suggested in part of the surgical staging procedures[5]. Fourth, we observed a proportion of non-adherence to PORT or denial of adjuvant radiotherapy. This issue should be explored and reviewed as we generally know that the adjuvant PORT improves OS and DFS, especially in either intermediate-risk or high-risk groups. Non-adherence to PORT is crucial in our regional context, the root cause should be investigated as it represents a missed opportunity to enhance patient outcomes. In 2021, the National Health Security Office (NHSO) announced the implementation of the Cancer Anywhere (CA) policy[21]. This program enabled access to radiotherapy in private hospitals in Chonburi and may offer potential strategies to mitigate prior constraints and improve survival outcomes in the future. Lastly, despite the survival outcome, the quality of life and the complications or sequelae from treatment also affect cancer survival patients[10, 22]. We look forward to exploring and conducting further studies on these issues in the future.

Conclusion

Patients with clinically early-stage cervical cancer who underwent surgery at Chonburi Hospital exhibited an overall 5-year survival rate of 85.3% and 5-year DFS of 84.0%. The FIGO 2018 stage beyond IB3, tumor size over 4 cm, LVSI, and deep stromal invasion were significant hazard clinicopathological factors for recurrence. In contrast, adjuvant PORT was the protective factor for recurrence.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Ruptured Primary Ovarian Pregnancy in Rural Setting: A rare case report

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ABSTRACT

Primary ovarian pregnancy is a rare type of ectopic pregnancy that has been associated with higher chance of rupture compared to other types. We present a 23-year-old woman with severe lower abdominal pain and 4 weeks amenorrhea. On physical examination, she was clinically unstable with distended abdomen and tenderness on palpation. Bimanual pelvic examination revealed cervical motion tenderness, left adnexal mass, and adnexal tenderness. Human chorionic gonadotropin test was positive, and transabdominal ultrasound showed no gestational sac in uterine cavity with massive fluid collection surrounding the uterus that hinder the identification of the ovaries. The exploratory laparotomy revealed a mass on the left ovary with active bleeding. Wedge resection was conducted, and histopathological examination showed chorionic villi and trophoblastic cells embedded in ovarian stroma, confirming the diagnosis of primary ovarian pregnancy. Differentiating ovarian pregnancy from tubal pregnancy, corpus luteum cyst, or ovarian endometrioma via ultrasound remains challenging.

Keywords: emergency, ectopic pregnancy, ovarian pregnancy, pregnancy complication.

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Introduction

Primary ovarian pregnancy is extremely rare form of ectopic pregnancy, with an approximately incidence of 0.15 - 3.5% of all ectopic pregnancy and 1 in 7,000 to 40,000 live births[1, 2]. Despite of being one of the rarest forms of ectopic pregnancy, it is reported to have a higher chance of rupture compared to tubal pregnancy, which is the most common form of ectopic pregnancy[3]. Therefore, preoperative diagnosis is crucial in the management of ovarian pregnancy to prevent poor outcomes and severe complications. However, it is challenging as the clinical presentations of ovarian pregnancy are frequently similar to tubal pregnancy, hemorrhagic corpus luteum, complicated ovarian cyst or granulosa cell tumor[4-6].

Hence, it is important to have an ovarian pregnancy as one of the differential diagnoses before proven otherwise. Herein, we present a case of ruptured ovarian pregnancy in a primigravida patient with no pre-existing risk factors.

Case report

A 23-year-old unmarried female was admitted to the hospital with severe abdominal pain and a history of amenorrhea for 29 days. She had associated symptoms of dizziness, nausea and several episodes of vomiting but there was no history of vaginal bleeding, loss of consciousness, urinary or gastrointestinal tract symptoms. The patient reported being sexually active and had not use any contraceptive methods. There was also no history of symptoms suggestive of pelvic inflammatory disease or other medical conditions. The patient admitted that she had never been pregnant before and had not undergone any previous surgery. There was no significant family history. On physical examination, she looked distressed and pale. Her body temperature was 36.5°C, blood pressure was 90/60 mmHg with a pulse rate of 116 beats per minute, and respiratory rate were 24 breaths per minute. The abdomen was distended and tender on palpation with muscular defence and rebound tenderness. The pelvic examination revealed cervical motion tenderness, left adnexal mass, adnexal tenderness and fullness in the pouch of Douglas. The bedside qualitative urine human chorionic gonadotropin (hCG) test was positive. Laboratory analysis revealed a decreased hemoglobin level (9.6 g/dL) and elevated white cell count (27,430 cells/μL). Transabdominal ultrasound showed normal uterus size with no gestational sac in the endometrial lining, massive fluid collection in the pouch of Douglas and surround the uterus and adnexa indicating hemoperitoneum, and no ovaries were able to be identified. Transvaginal ultrasound could not be performed due to the unavailability of the probe in primary care settings. Additionally, the patient's condition was deteriorating, making it impossible to undergo another ultrasound examination.

Based on these findings, patient was suspected of having a ruptured ectopic pregnancy. After securing blood products and obtaining informed consent, an emergency exploratory laparotomy was conducted. An 8 - 10 cm Pfannenstiel incision was made two fingerbreadths above the pubic bone. Approximately 1,200 ml of blood and blood clots was present at the peritoneal cavity which was then aspirated. After lavage, we found an approximately 2x2 cm mass on the left ovary with active bleeding. Both fallopian tubes and right ovary appeared normal (Fig. 1).

Wedge resection was then performed, and the extracted tissue was sent for histopathological analysis. During the operation, the patient received two packed red blood cells. The patient remained hemodynamically stable during the postoperative period and was discharged on the second postoperative day. The histopathological examination revealed a predominantly hemorrhagic area containing chorionic villi and trophoblastic cells embedded in ovarian stroma, which was consistent with the finding of primary ovarian ectopic pregnancy (Fig. 2).

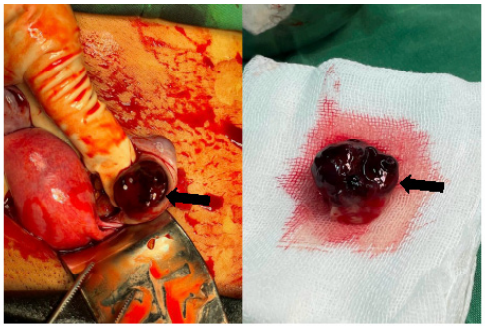

Fig. 1. Intraoperative findings of a ruptured primary ovarian pregnancy; a gestational sac in the left ovary (arrow).

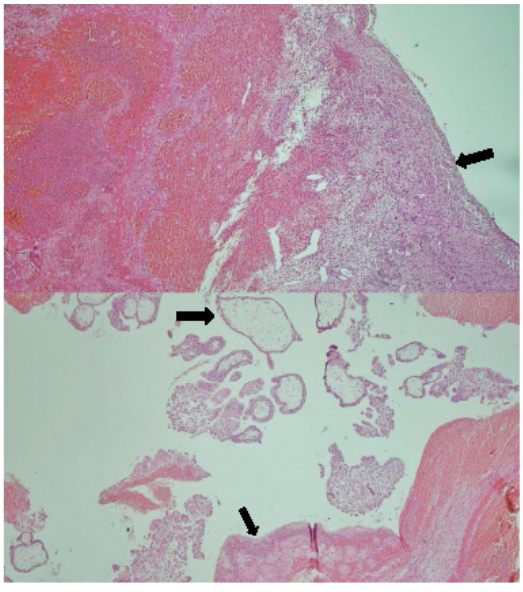

Fig. 2. Histopathology result of the specimen; section shows chorionic villi, and trophoblastic cells are embedded in left ovarian stroma (arrow) [hematoxylin and eosin stain at magnification of 40 X]

Discussion

Ovarian pregnancy is a rare type of ectopic pregnancy which the gestational sac is implanted and developed in ovary. The implantation anomaly is suggested due to the defective follicular extrusion or disruption of ovum transport pathway, which then causes fertilization of the ovum in the peritoneal cavity and implantation on the surface of the ovary[7, 8]. Although the exact cause of ovarian pregnancy is unknown, there are several risk factors that may be associated with this condition, such as use of an intrauterine device, assisted reproductive technology, multipara, history of pelvic inflammatory disease, and history of pelvic or abdominal surgery[9,10]. However, the reported patient did not have these risk factors. This finding was similar to other studies in which most cases of ovarian pregnancy can occur without having any risk factors[10,11]. Despite the low incidence of

ovarian pregnancy, it is among the leading causes of maternal morbidity and mortality in the first trimester[12]. The ovary consists of abundant blood vessels and lacks muscle fibers, which make it easier to rupture and lead to intraabdominal hemorrhage and hypovolemic shock. A ruptured ovarian pregnancy commonly present with sudden severe abdominal pain, dizziness, and syncope, which was the case in the reported patient[3, 6]. Therefore, an early diagnosis and immediate intervention were the key to produce better prognosis.

Preoperative diagnosis is usually done clinically with the supporting data from biochemical and ultrasound findings. Combination of the ectopic pregnancy's classic clinical triad (abdominal pain, vaginal bleeding, and amenorrhea) along with elevated βhCG level, and the absence of gestational sac in the uterus on ultrasound is sufficient to consider ectopic pregnancy as a differential diagnosis[10]. However, it is often challenging to differentiate an ovarian pregnancy from a tubal pregnancy, corpus luteum cyst, or ovarian endometrioma sonographically[4, 6].

Comstock et al proposed an ultrasound diagnostic criteria for ovarian pregnancy, which are the following: a large echogenic ring with an internal echolucent area on the surface of the ovary, the ring has a greater echogenicity than the ovary, and the investigated mass is surrounded by ovarian cortex, including follicles and corpus luteum[13]. Unfortunately, it is almost impossible to diagnose a ruptured ovarian pregnancy preoperatively using ultrasound because the formation of blood clot can hinder identification of the ovaries, which was the case in this patient[6].

The ultrasound examination of this patient was also unable to clearly identify the ovaries, thus the diagnosis had to be made intraoperatively and confirm postoperatively as in most cases of ovarian pregnancies. The Spiegelberg's criteria are used to diagnose ovarian pregnancy, which is a combination of anatomic and histopathological findings. These are the following criteria: the ipsilateral fallopian tube and fimbria must be intact and separate from the ovary, the gestational sac must occupy the normal position of ovary, the ovary and gestational must be attached to uterus through the ovarian ligament, the ovarian tissue must be present in the wall of gestational sac and proven histologically[14]. In this case, the Spigelberg's criteria were met thus the diagnosis of ovarian pregnancy was concluded.

Primary ovarian pregnancy refers to the implantation of a fertilized ovum on the outer surface of the ovary. This type of pregnancy typically ends in rupture during the first three months. Primary ovarian pregnancy typically occurs due to ovulatory dysfunction, where the ovum is fertilized while still inside the follicle before it is expelled from the ovary. In contrast, secondary ovarian ectopic pregnancy refers to the occurrence of fertilization within the fallopian tube, followed by the conceptus being expelled and implanted in the ovarian stroma[15].

Roy et al found that cases of secondary ovarian pregnancy can be established when there is evidence of a previous ectopic pregnancy in the fallopian tube which then regurgitates implantation into the ovary. In this case, they found a tubo-ovarian mass which was then subjected to histopathological examination of the tubo-ovaries and found a trophoblastic tissue in both the ovary and fallopian tube of the location of the ectopic pregnancy. This supports the diagnosis of secondary ovarian pregnancy[16]. In our case, we did not find any abnormality or tubal abortus mass in both fallopian tubes, so histopathological examination of the fallopian tubes was not done, considering the fertility of the patient. In addition, the Spielberg criteria were all met in our case. Hence, a diagnosis of primary ovarian pregnancy was made.

The management of ruptured ovarian pregnancy is done surgically with the primary goal to remove the ectopic pregnancy while preserving the ovary tissue. It can be accomplished by dissection of trophoblast off the ovary or ovarian wedge resection. In the case of excessive bleeding or coexisting ipsilateral ovarian

pathology or a request for removal of the ovary from the patient, an oophorectomy may be performed[10,17]. In this case we performed an emergency laparotomy because the site of the ectopic pregnancy could not be identified preoperatively along with the signs of circulatory collapse indicating the need for urgent management. An ovarian wedge resection was done to preserve the future fertility.

Several case reports have addressed primary ovarian pregnancy, and we present a case identified in a primary care setting that meets the Spielberg criteria for primary ovarian ectopic pregnancy as in the case of Phupong et al, which was also confirmed by histopathology[18]. In the case reported by Meethong et al, histopathological examination was not performed leading to an uncertain diagnosis as the Spielberg criteria were not fulfilled[19]. For the management of ovarian pregnancy, some studies have reported performing laparoscopic surgery[20, 21]. However, these procedures can be challenging due to the risk of significant intraabdominal bleeding, which can obstruct visualization, as demonstrated in this case. Additionally, our patient presented with hemodynamic instability, necessitating urgent intervention[11]. Therefore, laparotomy is still relevant in such emergency cases as in our case and Bharti et al[22].

In the cases of ruptured ovarian pregnancy, urgent management are often required which can lead to more frequent misdiagnosis due to its rarity. This case report accentuates the importance of considering an ovarian pregnancy as a differential diagnosis in patients presenting with classic signs of ectopic pregnancy.

Potential conflicts of interest

The authors declare no conflicts of interest.

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