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Thai Journal of Obstetrics and Gynaecology
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EDITORIAL

This second issue of Thai Journal of Obstetrics and Gynaecology 2024 contains many interesting articles. One special article is "Lifestyle Factors and the Risk of Endometrial Cancer: A Review". The contents include the impact of lifestyle factors such as diet, obesity, alcohol, physical activity and smoking on the risk of endometrial cancer.

The quality of Thai Journal of Obstetrics and Gynaecology (TJOG) has been improved. In the year 2023, TJOG received the Q3 journal rankings (149/203 journals) with SJR score 0.158 in Obstetrics and Gynaecology category from Scimago Journal & Country Rank 2022. TJOG has been indexed in many databases: Scopus, TCI, ASEAN Citation Index, DOAJ, EuroPub, and Google Scholar. The Editorial Board of TJOG looks forward to continuously raising the quality of the TJOG.

RTCOG midyear Meeting 2024 will be held during 23-26 April 2024 at Centara Grand at Central Plaza Ladprao Bangkok, Thailand. The theme of this meeting is "Smart Strong Sustainable OB&GYN". All RTCOG members are cordially invited to participate in this scientific meeting.

Wish to see you at RTCOG midyear Meeting 2024 at Centara Grand at Central Plaza Ladprao Bangkok, Thailand

Prof. Vorapong Phupong, M.D.
Editor in Chief

Thai Journal of Obstetrics and Gynaecology
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SPECIAL ARTICLE

Lifestyle Factors and the Risk of Endometrial Cancer: A review

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ABSTRACT

Endometrial cancer (EC) is among the most prevalent gynecologic cancers worldwide, experiencing a significant surge in incidence of approximately 60% over the past three decades. Addressing this growing burden involves three primary strategies: EC screening, lifestyle modification, and chemoprevention. Compelling evidence underscores the role of healthy lifestyle changes embracing a nutritious diet, abstaining from alcohol consumption, and regular physical activity (PA) in mitigating not only the risk of cardiovascular diseases but also overall non-cancer mortality in the general population. Moreover, heightened attention from researchers in recent decades has focused on understanding the connection between adopting healthy lifestyle factors and diminishing the risk of various cancers. In the case of EC, current epidemiological findings highlight that modifiable factors such as PA and diet may be linked to a reduced risk of this cancer. This review aims to comprehensively examine and synthesize the latest evidence pertaining to the influence of lifestyle factors and behaviors on the risk of EC, shedding light on actionable insights for risk reduction and preventive measures.

Keywords: endometrial cancer, lifestyle, modification, prevention, risk factor.

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Introduction

Cancer is a leading public health and economic issue worldwide. According to estimates from the International Agency for Research on Cancer, more than 19.0 million newly diagnosed cases of cancer and nearly 10.0 million deaths due to cancer occurred in 2020. Projections indicate that the worldwide incidence of cancer is expected to surge to 28.4 million cases by 2040, representing a substantial 47% increase compared to the statistics recorded in 2020[1].

The burden of cancer expands beyond death from the disease. Individuals affected by a cancer diagnosis experience physical and psychological distress. They also face a decline in their quality of life, which is often related to disease symptoms, investigative procedures, and adverse effects of cancer treatment[2]. The risk factors for cancer are closely associated with population growth, social development, and environmental changes. The evolution of society is inherently linked to lifestyle or behavior changes that contribute to metabolic diseases such as dyslipidemia, hypertension, obesity, insulin resistance, and type 2 diabetes mellitus (DM), potentially increasing the risk of cancer[3-4].

In 2005, information from the World Health Organization revealed that more than one in every three (35%) of the 7 million cancer-related deaths worldwide could be attributed to nine potentially modifiable risk factors, such as lack of physical activity (PA), obesity, cigarette smoking, alcohol use, and an unhealthy dietary pattern. Consequently, the predominant factors influencing global cancer occurrence and mortality are modifiable lifestyle risk factors[5-6]. Nowadays, governmental authorities and prominent non-profit health organizations, including the American Cancer Society (ACS) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), have outlined international public health guidelines and recommendations[2, 7-8]. These emphasize a healthy diet, reduced alcohol consumption, achieving a healthy body weight, and physical fitness for the prevention of cancer.

Endometrial cancer (EC) is one of the leading cancers in women around the world, with 417,000 new diagnoses reported globally in 2020[1,8]. The number of diagnoses has increased by approximately 60% in the past three decades due to shifting demographics, specifically an aging population, an uptick in obesity rates, and a decrease in hysterectomies conducted for non-malignant reasons[9]. As we know, established risk factors for elevated EC risk include obesity, unopposed estrogen exposure, and nulliparity[10]. Additionally, lifestyle factors, such as insufficient PA and a diet high in glycemic content, emerge as significant contributors to EC risk[2, 11-12]. The role of lifestyle modification in the prevention of EC has been established over the past several decades[11]. Growing evidence from both experimental and epidemiological research suggests that lifestyle factors, which can be modified, may impact the risk of EC[11-14]. A systematic review and meta-analysis of four cohort studies and one case-cohort study revealed a negative association between adherence to cancer prevention guidelines (including WCRF/AICR or ACS guidelines) and the risk of EC[13]. In addition, a recent multicentric case–control study demonstrated that higher adherence to the WCRF/ AICR recommendations on body fatness, PA, and diet was associated with about 60 % reduced risk of EC. The study also identified that body weight had the most significant impact on the risk. Therefore, continuing a healthy body weight throughout one's lifetime is the essential suggestion for EC prevention[15]. In this review, our aim is to summarize the most recent evidence regarding the impact of lifestyle factors or behaviors on the risk of EC.

The influence of diet

Bioactive components present in everyday foods have the potential to enhance interactions with chronic inflammation. This may stimulate cell proliferation, inhibit apoptosis, and trigger the secretion of mediators that could lead to carcinogenesis and malignant transformation of cells[16-17]. Numerous investigations have explored the connection between diet and EC risk. For instance, a case-control study in Japan, involving 161 cases and 380 controls, examined the association between food intake and endometrioid EC. The study revealed that a higher intake frequency of vegetables, fish, and boiled eggs was associated with a reduced risk, while higher intake frequency of convenience foods and fried foods showed a positive effect compared to lower levels in the risk of EC[18]. These findings align with a recent meta-analysis of six cohort studies and twenty-one case-control studies, indicating that vegetables

(pooled odds ratio [OR]=0.76), cruciferous vegetables (pooled OR=0.81), dark green and yellow/orange combined vegetables (pooled OR=0.64), and fruits (pooled OR=0.81) were strongly associated with a reduced risk of EC[19].

The International Agency for Research on Cancer has recently reclassified processed meat as a Group 1 carcinogen and red meat as a Group 2A probable carcinogen[20]. Additionally, in relation to the impact of estrogen-containing compounds in animal food on the risk of EC, a systematic review and meta-analysis discovered that the consumption of meat, especially red meat, raises the risk EC[21].

As we are aware, the consumption of sugar-sweetened beverages (SSB) constitutes a significant risk factor for obesity and type 2 DM[22]. However, research attention on the correlation between SSB consumption and the risk of cancer has been limited. The potential mechanism may revolve around their role in promoting tumor cell growth and cell proliferation[22-24]. A population-based cohort study conducted in the United States of America revealed the association between SSB intake and EC risk in 23,039 postmenopausal women. The study demonstrated that elevated consumption of SSB and sugars was linked to a higher risk of type I EC. However, no such association was identified in type II EC[23]. In addition, a recent case-cohort study from Canada also found that SSB intake and/or fruit juice intake are associated with a higher risk of EC[24].

Experimental and laboratory studies have indicated that green tea and coffee possess anticarcinogenic and chemopreventive properties[25-26]. The association between coffee/caffeine consumption and a decreased risk of EC has been confirmed in several previous studies, including a meta-analysis of twelve prospective cohort studies[25-27]. According to the findings of the meta-analysis, increasing coffee intake by four cups per day was linked to a 20% decrease in the risk of EC and a 24% decrease in postmenopausal cancer risk[27]. In certain studies, there has been a connection between green tea consumption and a decreased risk of EC[25,28], although conflicting findings exist in other studies[26,29].

The influence of obesity

There is evidence that obesity is a significant global health issue and is associated with many metabolic diseases such as hypertension and type 2 DM. Moreover, it is associated with an increased risk and adverse prognostic factors for several types of cancers, including breast, endometrial, and cervical cancers[11, 25, 30-31]. According to findings from a meta-analysis, each increment of 5 body mass index (BMI) units corresponds to a 50% rise in the risk of developing EC[31]. Data from a comprehensive population-based study in Europe revealed that women classified as overweight (BMI 25.0-29.9 kilogram [kg]/meter [m]^2) before the age of 40 had hazard ratios (HR) for EC of 1.70[32]. Furthermore, a substantial nationwide cohort study in Japan indicated that, upon adjusting for potential confounding factors, a BMI exceeding 23.0 kg/m^2 exhibited a linear association with the risk of EC, with the HR per 5 kg/m^2 increase being 1.80. An increase in weight by ≥ +5 kg since the age of 20 was associated with a heightened risk of EC compared to a weight change within the range of -5 to < +5 kg (HR=1.96)[33]. Lastly, a systematic and meta-analysis reported a 60% decrease in the likelihood of developing EC after bariatric surgery, which involves surgical interventions leading to substantial weight loss. This reduction was observed in comparison to controls who did not undergo surgery (relative risk [RR] = 0.4)[34].

The connection between obesity and EC involves a complex system comprising multiple interconnected pathways and mechanisms. Adiposity impacts not just metabolism but is strongly correlated with conditions like hyperlipidemia, insulin resistance, hyperglycemia, and hyperinsulinemia. The components of fat tissue exhibit both pro- and anti-inflammatory characteristics, serving as a source of hormone production and playing a crucial role in endometrial proliferation[31,35].

The influence of alcohol

The association between alcohol intake and EC has been under investigation for many years, yielding inconclusive results. Earlier epidemiological studies have identified a correlation between alcohol consumption and increased levels of circulating estrogens in women, implying a potential elevation in the risk of EC[36-37]. Nevertheless, moderate alcohol intake has been linked to beneficial effects on the adiponectin inflammatory marker and insulin sensitivity, potentially reducing the risk of EC[38]. Despite these findings, the majority of epidemiological and meta-analysis studies consistently report no association between alcohol consumption and EC risk[25, 39-42].

The influence of physical activity

Growing epidemiological evidence suggests that engaging in PA could lower the risk of cancer, including EC[11-12, 14,43]. Moore et al. conducted a meta-analysis of nine prospective studies to determine the association of PA and EC risk. They discovered that recreational PA was significantly linked to a decreased risk of EC, with active women having a roughly 30% lower risk than inactive women[14]. A large-scale nationwide cohort study in Japan suggests that compared to women who were mainly sitting at the worksite, those who were mainly standing (HR=0.79) and moving (HR=0.46) had a lower risk (P for trend=0.042)[33]. Additionally, recent data from a systematic review and meta-analysis of fourteen studies reported a 55% increased risk of EC among individuals with higher levels of total sedentary behavior (RR=1.55), a 22% increase among those with higher levels of occupational sedentary behavior (RR=1.22) and a 34% increase with borderline significancy among those with higher levels of leisure-time sedentary behavior (RR=1.34). The overall increased risk disregarding specific domains was 27% (RR=1.28)[44]. Current recommendations from the ACS for diet and PA for cancer prevention suggest that adults should engage in 150-300 minutes of moderate-intensity PA per week, or 75-150 minutes of vigorous-intensity PA, or an equivalent combination; achieving or exceeding the upper limit of 300 minutes is optimal[2].

Several hypotheses have been proposed to elucidate the reduced risk of EC associated with PA. PA may contribute to the reduction of serum estradiol levels and the increases of sex hormone binding globulin, the binding protein for estradiol. Additionally, it might lead to lower levels of reactive oxygen species, enhanced immune function, reduced inflammation, and improved insulin sensitivity[14, 43]. These beneficial effects of PA may also be mediated through prevention of weight gain[14].

The influence of smoking

It is now well established that cigarette smoking increases the risk of developing cardiovascular and respiratory tract diseases. Cigarette smoking also increases the risk of various cancers, including lung, nasopharynx, bladder, and cervical cancers[45]. Conversely, cigarette smoking is associated with a lower risk of EC[25, 46-47]. A meta-analysis of ten prospective and twenty-four case-control studies reported that overall, smoking was statistically significantly associated with 18% and 29% reduced risks of EC in prospective and case-control studies, respectively[46]. Dimou et al. recently conducted an extensive multicenter observational study to thoroughly investigate the connection between smoking and the risk of EC. Their findings in the observational analysis revealed an association between a lifetime amount of smoking and regular smoking with a lower risk of EC. However, in the Mendelian randomization analysis, considering BMI and a genetic predisposition to a higher lifetime amount of smoking, there was no association observed with EC risk[47].

The potential mechanism that could explain this association involves antiestrogenic effects[25,46]. Smoking is also linked to an earlier age at menopause, and as a result, it may reduce the risk of developing EC due to decreased exposure to endogenous circulating estrogen levels[47].

Conclusion

EC stands out as a major concern in women's health, marked by a growing number of diagnoses, investigations, and treatments attributed to the increase in life expectancy and the rise in obesity rates. Additionally, unhealthy lifestyle behaviors, such as a lack of PA and a diet or beverage high in sweet sugar content, emerge as significant contributors to EC risk. Therefore, it is prudent to provide lifestyle recommendations focused on mitigating EC risk, such as increasing PA, maintaining a healthy body weight, and adopting a balanced diet rich in vegetables and fish, to all women. Discussing specific preventive strategies during counseling and personalized risk assessment is crucial. Moreover, implementing effective cancer prevention recommendations or guidelines for everyone, including women, may lead to a lower incidence of EC.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Diagnostic Accuracy of the Foetal Umbilical Artery, Middle Cerebral Artery Doppler Indices and Cerebroplacental Ratios for Predicting Adverse Perinatal Outcomes in Pregnancy-induced Hypertension

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ABSTRACT

Objectives: This study aimed to evaluate the accuracy of the foetal umbilical artery, middle cerebral artery Doppler indices and cerebroplacental ratios to predict adverse perinatal outcomes in pregnancy-induced hypertension.

Materials and Methods: This study was a diagnostic test. The study population comprised 76 women with singleton pregnancies (32-40 weeks gestation) diagnosed with pregnancy-induced hypertension who were admitted to Hatyai Hospital between December 2020 and November 2022. Diagnostic accuracy for all Doppler measurements was evaluated using sensitivity, specificity, accuracy and positive likelihood ratio (LR+) analysis.

Results: The umbilical artery pulsatility index (UA PI) had the highest sensitivity for predicting adverse perinatal outcomes at 80% for predicting neonatal intensive care unit (NICU) admissions ($p = 0.044$), though the Umbilical arterial systolic/diastolic (UA S/D) ratio, The fetal middle cerebral artery pulsatility index (MCA PI) and cerebroplacental ratio (CPR) were poor predictors of NICU admissions ($p > 0.05$). The MCA PI could better predict all perinatal outcomes with LR+ 4.29 ($p = 0.003$).

Conclusion: Fetal umbilical artery Doppler; Middle cerebral artery Doppler; Cerebroplacental ratio, Perinatal outcomes, Pregnancy-induced hypertension

Keywords: fetal umbilical artery Doppler, middle cerebral artery Doppler, cerebroplacental ratio, perinatal outcomes, pregnancy-induced hypertension.

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การวัดเส้นเลือดแดงบริเวณสายสะดือและเส้นเลือดแดงบริเวณสมองทารกในครรภ์ร่วมกับการวัดค่าอัตราส่วนแรงต้านทานระหว่างเส้นเลือดแดงบริเวณสมองกับเส้นเลือดแดงบริเวณสายสะดือทารกเพื่อทำนายผลลัพธ์การคลอดของทารกที่ไม่พึงประสงค์ในหญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์

พักตร์ประภา ไชยภักดี

บทคัดย่อ

วัตถุประสงค์: *เพื่อหาความแม่นยำของการใช้เส้นเลือดแดงบริเวณสายสะดือและเส้นเลือดแดงบริเวณสมองทารกในครรภ์ร่วมกับการวัดค่าอัตราส่วนแรงต้านทานระหว่างเส้นเลือดแดงบริเวณสมองกับเส้นเลือดแดงบริเวณสายสะดือทารกเพื่อทำนายภาวะทุพพลภาพของทารกหลังคลอดและทารกตายปริกำเนิดในหญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบทดสอบวินิจฉัยความแม่นยำของการใช้เส้นเลือดแดงบริเวณสายสะดือและเส้นเลือดแดงบริเวณสมองทารกในครรภ์ร่วมกับการวัดค่าอัตราส่วนแรงต้านทานระหว่างเส้นเลือดแดงบริเวณสมองกับเส้นเลือดแดงบริเวณสายสะดือทารกเพื่อทำนายภาวะทุพพลภาพของทารกหลังคลอดโดยทำในสตรีตั้งครรภ์เดี่ยวช่วงอายุครรภ์ตั้งแต่ 32 ถึง 40 สัปดาห์ ที่ได้รับการวินิจฉัยว่ามีภาวะความดันโลหิตสูงขณะตั้งครรภ์ ณ โรงพยาบาลหาดใหญ่ ระหว่างเดือนธันวาคม พ.ศ.2563 ถึงเดือนพฤศจิกายน พ.ศ.2565 โดยวิเคราะห์เป็น ความไว ความจำเพาะ ความแม่นยำ และอัตราส่วนความน่าจะเป็น*

ผลการศึกษา: *เส้นเลือดแดงบริเวณสายสะดือทารกในครรภ์ (UA PI) ช่วยทำนายภาวะเข้ารับการรักษาที่ห้องอภิบาลทารกแรกเกิดภาวะวิกฤติได้ดีที่สุดเมื่อเทียบกับเส้นเลือดอื่นๆ โดยมีความไวร้อยละ 80 นอกจากนี้เส้นเลือดแดงบริเวณสมองทารกในครรภ์ (MCA PI) ยังช่วยทำนายผลลัพธ์การคลอดของทารกโดยรวมได้ดีที่สุด (LR+=4.29)*

สรุป: *เส้นเลือดแดงบริเวณสายสะดือทารกในครรภ์ (UA PI) ช่วยทำนายภาวะเข้ารับการรักษาที่ห้องอภิบาลทารกแรกเกิดภาวะวิกฤติได้ดีที่สุด นอกจากนี้ MCA PI ยังช่วยทำนายผลลัพธ์การคลอดของทารกโดยรวมได้ดีที่สุด (LR+=4.29)*

คำสำคัญ: *เส้นเลือดแดงบริเวณสายสะดือทารกในครรภ์, เส้นเลือดแดงบริเวณสมองทารกในครรภ์, อัตราส่วนแรงต้านทานระหว่างเส้นเลือดแดงบริเวณสมองกับเส้นเลือดแดงบริเวณสายสะดือทารก, ผลลัพธ์การคลอดของทารกที่ไม่พึงประสงค์, ภาวะความดันโลหิตสูงขณะตั้งครรภ์*

Introduction

Pregnancy-induced hypertension (PIH) is the novel onset of hypertension after 20 weeks of gestation and typically returns to normal by 12 weeks postpartum. PIH criteria include gestational hypertension, preeclampsia and chronic hypertension with superimposed preeclampsia[1]. PIH is one of the most common causes of both maternal and neonatal morbidity, affecting about 5-10 % of pregnant women. The incidence of PIH at Hatyai Hospital is about 5 %.

The pathogenesis of PIH has not yet been fully elucidated. However, PIH is associated with reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles, which may affect intrauterine growth restriction (IUGR), foetal hypoxemia and foetal death[2].

Uteroplacental and fetoplacental circulation can be studied effectively by Doppler ultrasound. Many studies have used foetal vascular Doppler tests, such as umbilical artery, middle cerebral artery indices and cerebroplacental ratios for the prediction of uteroplacental insufficiency and perinatal mortality[3-9].

Despite the aforementioned, few studies in Thailand have focused on foetal Doppler research for the prediction of adverse perinatal outcomes in PIH and the results of previous studies remain inconclusive. Therefore, the objective of this study was to assess the accuracy of the foetal umbilical artery and middle cerebral artery Doppler indices and cerebroplacental ratios were used to predict adverse perinatal outcomes, including neonatal intensive care unit (NICU) admission, and Apgar score < 7 at 5 minutes in PIH. This study was the first in Southern Thailand, which can be used to predict adverse perinatal outcomes in intrauterine growth restriction (IUGR) foetus that has birth weight below the 10th percentile for its gestational age or failing to reach its genetically predetermined growth potential. The prediction of adverse outcomes can be used to counsel patients and help clinicians make decisions concerning the time of delivery, Additionally, it can help to notify NICU teams early for neonatal resuscitation.

Materials and Methods

This study was a diagnostic test. Approval for this research was received by the Institutional Review Board of Hatyai Hospital. The study population included 76 women with singleton pregnancies who were diagnosed with PIH at 32-40 weeks of gestation and were admitted to Hatyai Hospital between December 2020 and November 2022. PIH criteria include gestational hypertension, preeclampsia and chronic hypertension with superimposed preeclampsia according to the ACOG 2019 guidelines. All patients were recruited consecutively and included pregnant women who had medical disorders as well as obstetric risk factors such as diabetes mellitus, chronic hypertension, gestational diabetes mellitus (GDM), obesity, abruptio placenta, large for gestational age (LGA), and myoma uteri, etc.

Patients who had intrauterine foetal death, multiple gestations or foetal anomalies were excluded.

The sample size was calculated by the prevalence of adverse perinatal outcomes based on previous studies[10]. Sensitivity and specificity were accepted following the study of Smitha[7], this study needed a sample size of 76 cases to gain power of 80% at 95% confidence interval (CI).

After informed consent was gained, all patients were advised according to the institutional guidelines. Transabdominal ultrasound tests were for foetal weight, amniotic fluid, placenta and Doppler study were done using a GE Voluson E6 ultrasound machine. Doppler waveform analyses of the umbilical artery and middle cerebral artery as well as calculation of cerebroplacental ratio were performed by single level II sonographer in a specialised maternal foetal medicine. The

waveforms were obtained during foetal inactivity and apnoea.

The umbilical artery pulsatility index (UA PI) was obtained from a free loop of cord, while the middle cerebral artery pulsatility index (MCA PI) was obtained at the level of the greater wing of the sphenoid at an angle of insonation near 0 (0-10 degrees). The flow velocity waveforms were computed automatically. Measurements were done three times and the average pulsatility index (PI), standard deviation (SD) were calculated[11].

The UA PI and systolic/diastolic ratio (UA-S/D) were considered abnormal when it was more than the 95th percentile of the reference range. Absent and reverse end diastolic flow of umbilical artery Doppler were considered abnormal.

The MCA PI was automatically calculated and considered abnormal when it was below the 5th percentile of the reference range.

The cerebroplacental ratio (CPR) was automatically calculated and considered abnormal when it was below the 5th percentile of the reference range[11].

Follow-up Doppler studies were performed weekly. The results of the last Doppler ultrasound within one week of delivery were used for analysis.

The collected data included demographic data, comorbidity, Doppler study (UA PI, UA S/D, MCA PI, and CPR) and neonatal outcomes such as fetal distress, intrauterine growth restriction (IUGR), large for gestational age (LGA), neonatal moderate care unit (NMCU) admission, Apgar score < 7 at 1and 5 minutes, The composite neonatal adverse outcome included NICU admission and Apgar score < 7 at 5 minutes.

Foetal distress was defined as category II and III foetal heart rate tracing according to the National Institute of Child Health and Human Development (NICHD) criteria. intrauterine growth restriction (IUGR) was diagnosed based on ultrasound parameters with estimated foetal weight being less than the 10th percentile for gestational age and umbilical Doppler PI > 95th percentile, while LGA was defined as estimated foetal weight being more than the 90th percentile for gestational age.

All data were collected from medical records at Hatyai Hospital.

Statistical analysis was done by Stata/SE for Windows Version 17 Stata Corp. Released 2021, StataCorp LLC College Station, Texas USA. Sensitivity, specificity, accuracy and positive likelihood ratio were calculated for the prediction of adverse perinatal outcomes. P values < 0.05 were considered statistically significant.

Results

Among 76 cases of PIH women, 43.42% had severe preeclampsia (PE) and 36.84% had gestational hypertension (GHT). A previous history of PIH was revealed in about 10.53%. The mean age of patients was 29.68 ± 6.89 years; most patients were less than 35 years old. About 40% of the patients were primigravida, and 38% of the patients were obese. Most of the patients (65.79%) were between 37 and 40 weeks of gestation at the time of Doppler examination and delivery. About 57 cases (75%) had less than a 24-hour interval for the time between assessment and delivery. Most patients (53.95%) had non-medical and obstetric risk factors.

Mode of delivery included vaginal (about 51.32%) and caesarean section (CS) (46.05%), with indications for CS including failed induction (14.47%), unfavourable cervix (13.16%), cephalopelvic disproportion (CPD) (9.21%), foetal distress (3.93%) and previous CS (2.63%). About 30.26% of patients had low birth weight (birth weight < 2,500 g). The data are shown in Table 1.

Table 1. Demographic and obstetric data for the studied patients (n = 76).

Characteristics	n (%)
Age (years)	
< 35	59 (77.63)
≥ 35	17 (22.37)
mean (SD)	29.68 (6.89)
Gravida	
Primi	31 (40.00)
Multi	45 (59.00)
BMI (kg/m^2)	
≥ 30	29 (38.16)
Gestational age at examination (weeks)	
32-36^{+6}	26 (34.21)
37-40	50 (65.79)
Type of PIH	
GHT	28 (36.84)
Mild PE	9 (11.84)
Severe PE	33 (43.42)
CHT with superimposed severe PE	6 (7.89)
Previous history of PIH	8 (10.53)
Medical and obstetric risk factors	
None	41 (53.95)
1	30 (39.47)
≥ 2	5 (6.58)
Gestational age at delivery (weeks)	
32-36^{+6}	26 (34.21)
37-40	50 (65.79)
Time interval between assessment and delivery (days)	
<1	57 (75.00)
1	10 (13.16)
≥ 2	9 (11.84)
Mode of delivery	
Vaginal	39 (51.32)
Caesarean section	35 (46.05)
Vacuum extraction	2 (2.63)
Indication of CS	
Foetal distress	3(3.95)
CPD	7(9.21)
Abnormal foetal presentation	4(5.26)
Failed induction	11(14.47)
Unfavourable cervix	10(13.16)
Previous CS	2(2.63)
COVID	1(1.32)
Birthweight (grams)	
< 2500	23 (30.26)
≥ 2500	53 (69.74)

SD: standard deviation, BMI: body mass index, PIH: pregnancy-induced hypertension, GHT: gestational hypertension, PE: preeclampsia, CS: caesarean section, CPD: cephalopelvic disproportion, COVID: coronavirus disease

All perinatal outcomes were experienced in approximately 55.26% and there were 28 cases (36.84%) with perinatal outcomes, including foetal distress, IUGR, NICU admission, NMCU admission,

and Apgar score < 7 at 1 and 5 minutes. Most of them were NMCU admission at 22.37%, and the second was IUGR at 15.79%. However, 6.58% of patients had NICU admission. The data are shown in Table 2.

Table 2. All perinatal outcomes (n = 42).

Outcome parameters	n (%)
Foetal distress	3 (3.95)
Intrauterine growth restriction	12 (15.79)
Neonatal intensive care unit admission	5 (6.58)
Neonatal moderate care unit admission	17 (22.37)
Apgar score at 1 minute < 7	4 (5.26)
Apgar score at 5 minutes < 7	1 (1.32)

There was a significant association between UA PI and NICU admission (p = 0.04). The UA PI could predict NICU admission with LR+ 2.58 and had the highest sensitivity (80%) when compared to other Doppler indices. However, the UA S/D ratio, CPR and MCA PI were poor predictors for NICU admission (p > 0.05). The data are shown in Table 3.

Table 3. Accuracy of Doppler indices for predicting NICU admission.

Doppler	Results	NICU (n=5)	Non-NICU (n=71)	p value *	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (%)	+ LR
UA PI	Abnormal	4	22	0.044	80.00	69.1	69.74	2.58
	Normal	1	49		(28.36, 99.49)	(56.92, 79.46)		
UA S/D	Abnormal	2	20	0.623	40.00	71.83	69.74	1.42
	Normal	3	51		(5.27, 85.34)	(59.90, 81.87)		
MCA PI	Abnormal	1	13	1.000	20.00	81.69	77.63	1.09
	Normal	4	58		(0.5, 71.64)	(70.73, 89.87)		
CPR	Abnormal	2	21	0.635	40.00	70.42	68.42	1.35
	Normal	3	50		(5.27, 85.34)	(58.41, 80.67)		

Values are given as a number, sensitivity, specificity, accuracy and likelihood ratio, Fisher's exact test (*)
NICU: neonatal intensive care unit, LR: likelihood ratio, CI: confidence interval, UA PI: umbilical artery pulsatility index, UA S/D: umbilical arterial systolic/diastolic, MCA PI: middle cerebral artery pulsatility index, CPR: cerebroplacental ratio

There were only 4 cases of Apgar score at 1 minute < 7. This study found that these Doppler indices (UA PI, UA S/D ratio, MCA PI and CPR) were not significantly associated with Apgar score at 1 minute < 7 (p > 0.05).

There were significant associations between MCA PI and the perinatal outcomes such as foetal distress, IUGR, NICU admission, NMCU admission, Apgar score at 1 minute < 7 and Apgar score at 5 minutes < 7 (p = 0.003). The MCA PI can predict the perinatal outcomes with LR+ 4.29 by sensitivity and specificity of 35.71% and 91.67%, respectively.

Discussion

Among pregnant women, PIH is associated with reduced uteroplacental perfusion as a result of the abnormal cytotrophoblast invasion of spiral arterioles, which may affect foetal growth restriction, foetal hypoxemia and foetal death[1]. Uteroplacental and fetoplacental circulation can be studied effectively by Doppler ultrasound. Many studies have used foetal vascular Doppler such as umbilical artery, middle cerebral artery indices and cerebroplacental ratios to predict uteroplacental insufficiency and perinatal mortality.

In the present study, the focus was on the accuracy of the foetal umbilical artery, middle cerebral artery Doppler indices and cerebroplacental ratios in women with third-trimester gestation with PIH to predict adverse perinatal outcomes (NICU admission and Apgar score < 7 at 5 minutes).

This study found that the UA PI could predict NICU admission with LR+ 2.58, similar to Alalfy et al[13] who showed the UA PI could predict NICU admission with LR+ 2.84. Moreover, this study found that the UA PI, UA S/D ratio, MCA PI and CPR indices were not associated with an Apgar score at 1 minute < 7.

This study showed that an MCA PI < 5th percentile could predict all perinatal outcomes with LR+ 4.29 (p = 0.003) more than other Doppler indices, similar to the observations made by Devi et al [14] and Lakhar et al[15]. The middle cerebral artery is the branch of the circle of Willis that carries 80% of the blood flow to the ipsilateral cerebral hemisphere, so it is a more sensitive parameter for foetal oxygenation status than umbilical blood flow[3, 7].

This study likewise found that the UA PI and CPR had the sensitivity (42.80 and 42.86%, respectively) to predict perinatal outcomes, similar to Gutierrez et al[16] and Fong et al[17].

This study was not correlated with Konwar et al[2], who reported that the CPR PI had more sensitivity (84.8%) than the current study (42.86%) for diagnosing perinatal outcomes. This may be due to the difference in the Doppler indices for examination and measurement. The Doppler indices in Konwar's study were obtained by manual plotting, while those in the current study were computed automatically. Moreover, the measurement for MCA PI angle and the abnormal reference of CPR PI were not similar to this study.

The results of the study can be applied for counselling patients with PIH about abnormal Doppler study to predict adverse perinatal outcomes as well as help with proper management.

The strength of this study was its complete delivery outcomes. There were no previous studies on foetal Doppler tests to predict adverse perinatal outcomes in pregnant women with PIH in Thailand. This research is presented as the first investigation in southern Thailand. Additionally, ultrasonography was performed only by the single level II sonographer to decrease interobserver variation. Still, there were some limitations of this study. Because this study was undertaken at a single centre that could not represent the general population, its results should be interpreted with caution when assessing the correlation between foetal Doppler study indices and adverse perinatal outcomes.

We suggest that future studies investigate the use of many centers and should use additional parameters such as clinical history combined with Doppler indices for better prediction of adverse perinatal outcomes.

Conclusion

The UA PI had the highest sensitivity for the detection of adverse perinatal outcomes (NICU admission). Furthermore, the MCA PI was the better predictor of perinatal outcomes.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Ibuprofen and Intraperitoneal Lidocaine Instillation for Relieving Intraoperative Pain during Postpartum Tubal Ligation via Minilaparotomy: A Randomized Controlled Trial

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ABSTRACT

Objectives: This randomized study evaluated the effects of preemptive ibuprofen, intraperitoneal lidocaine instillation, or both for pain relief during postpartum tubal ligation (PPTL) via minilaparotomy.

Materials and Methods: Ninety-two heathy mothers who opted for PPTL were randomized into four groups and received either 400 mg of oral ibuprofen and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution (Group I), oral placebo and intraperitoneal instillation of 20 ml of 1% lidocaine 20 ml (Group L), both ibuprofen and intraperitoneal instillation lidocaine (Group IL), or placebo and intraperitoneal isotonic sodium chloride solution (Group P).

Results: The mean intraoperative numerical rating scale (NRS) in group IL was significantly lower than in group P (mean difference -2.48, 95% CI -4.47 to -0.49, p = 0.007). No significant difference was found in the intra-operative NRS between groups I and L when compared to group P (mean difference -1.61 [95% CI -3.60 to 0.38], and 0.70 [95% CI -1.29 to 2.69], respectively), nor was there any significant difference in pain score immediately or one-hour post-operation.

Conclusion: Preemptive ibuprofen and intraperitoneal lidocaine instillation alone did not provide effective pain relief for postpartum tubal resection. However, multimodal analgesia using both agents was effective as intra-operative (but not post-operative) pain control.

Keywords: ibuprofen, intraperitoneal lidocaine, NSAIDs, postpartum tubal resection, sterilization.

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ไอบูโพรเฟนและการหยอดยาลิโดเคนในช่องท้องเพื่อบรรเทาอาการปวดระหว่างการทำหมันหลังคลอดโดยการผ่าตัดแบบเปิดหน้าท้องขนาดเล็ก: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

เจน โสธรวิทย์, ญาดา จารุอมรจิต, นันทสิริ เอี่ยมอุดมกาล, วรลักษณ์ สมบูรณ์พร, ศรีนารี แก้วฤดี

บทคัดย่อ

วัตถุประสงค์: *การศึกษาแบบสุ่มนี้ประเมินผลของไอบูโพรเฟนก่อนการผ่าตัด การหยอดยาลิโดเคนในช่องท้อง หรือทั้งสองอย่างในการบรรเทาอาการปวดระหว่างการทำหมันหลังคลอด โดยการผ่าตัดเปิดหน้าท้องขนาดเล็ก*

วัสดุและวิธีการ: *มารดาที่มีสุขภาพแข็งแรงจำนวน 92 รายที่เลือกการทำหมันหลังคลอด ได้รับการสุ่มออกเป็นสี่กลุ่ม และได้รับไอบูโพรเฟนแบบรับประทาน 400 มก. และการหยอดสารละลายไอโซโทนิกโซเดียมคลอไรด์ 20 มล. (กลุ่มที่ I) ยาหลอกแบบรับประทาน และการหยอดยา 1 % ลิโดเคน 20 มล. เข้าช่องท้อง (กลุ่ม L) ทั้งไอบูโพรเฟนและลิโดเคนแบบหยอดยาในช่องท้อง (กลุ่ม IL) หรือยาหลอกและสารละลายไอโซโทนิกโซเดียมคลอไรด์ในช่องท้อง (กลุ่ม P)*

ผลการศึกษา: *ค่าเฉลี่ยระดับคะแนนความปวดแบบตัวเลข (numerical rating scale) ในกลุ่ม IL ต่ำกว่ากลุ่ม P อย่างมีนัยสำคัญ (ความแตกต่างเฉลี่ย -2.48, 95% CI -4.47 ถึง -0.49, p = 0.007) ไม่พบความแตกต่างอย่างมีนัยสำคัญในคะแนนความปวดแบบตัวเลขระหว่างผ่าตัดระหว่างกลุ่ม I และ L เมื่อเปรียบเทียบกับกลุ่ม P (ความแตกต่างเฉลี่ย -1.61 [95% CI -3.60 ถึง 0.38] และ 0.70 [95% CI -1.29 ถึง 2.69] ตามลำดับ) และไม่มีความแตกต่างอย่างมีนัยสำคัญในคะแนนความเจ็บปวดทันทีหรือหลังการผ่าตัดหนึ่งชั่วโมง*

สรุป: *การให้ไอบูโพรเฟนล่วงหน้าหรือหยอดยาลิโดเคนในช่องท้องเพียงอย่างเดียวไม่ได้ช่วยบรรเทาอาการปวดอย่างมีประสิทธิภาพสำหรับการผ่าตัดทำหมันหลังคลอด อย่างไรก็ตาม การระงับปวดแบบพหุวิธีโดยใช้ยาทั้งสองชนิดมีประสิทธิผลในการควบคุมความเจ็บปวดระหว่างการผ่าตัด (แต่ไม่ใช่หลังการผ่าตัด)*

คำสำคัญ: *ไอบูโพรเฟน, ลิโดเคนในช่องท้อง, NSAIDs, การผ่าตัดท่อนำไข่หลังคลอด, การทำหมัน*

Introduction

Tubal ligation is a method of permanent contraception with a failure rate of less than 1%.1 Globally, it is one of the most common methods of contraception[2]. Minilaparotomy is an attractive option for postpartum tubal ligation (PPTL) due in part to its safety and short required operative time[3]. However, this procedure can involve varying degrees of pain and discomfort. This can be considered as a significant obstacle for women opted for PPTL. Pain management therefore is crucial to the procedure's success and can be provided via general, regional, or local anesthesia[4]. Although general and regional anesthesia are highly effective[5], they require an anesthesiologist and are relatively costly compared to local anesthesia. As a result, they are not always practicable, particularly in low-resource settings[6].

Although various local analgesics are available for intraoperative pain relief, few have been investigated. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin production by inhibiting cyclooxygenase (COX) enzyme[7]. Ibuprofen is a preferred NSAID for postpartum/lactating women due to its particularly low concentrations in breastmilk and short half-life[8]. This makes ibuprofen an attractive possible choice for pain relief in PPTL. A recent systematic review on intervention for pain control during PPTL reported only three randomized controlled trials (RCTs) evaluating lidocaine instillation and intramuscular morphine, either alone or in combination4 and none evaluating the effectiveness of NSAIDs.

Preemptive analgesia is the introduction of antinociceptive treatment prior to painful stimuli[9]. This approach to pain management is considered promising for surgery, as the timing of the painful stimulus is known. The objective of this study was to explore the effectiveness of preemptive ibuprofen and intraperitoneal lidocaine for pain management in PPTL.

Materials and Methods

This randomized, double-blinded, placebo-controlled study was conducted at Srinagarind Hospital, a university hospital in northeast Thailand, from March 2021 to April 2022. It was approved by The Khon Kaen University Ethics Committee for Human Research (HE631087). The trial was also registered with www.thaiclinicaltrials.org (TCTR20200712001). Healthy women aged 18-45 years who (a) delivered within 72 hours before tubal ligation, (b) desired permanent contraception, (c) had American Society of Anesthesiologists (ASA) physical status of I[10], (d) had no contraindication for surgery, and (e) had given consent for PPTL were eligible for this study. We excluded women with (a) body mass index (BMI) ≥ 30 kg/m^2, (b) previous pelvic inflammatory disease or pelvic surgery, (c) contraindications for ibuprofen, or (e) lidocaine allergy. We followed the CONSORT guideline[11].

After obtaining written informed consent, participants were randomly assigned to one of four groups. Group I (Ibuprofen) received 400 mg of oral ibuprofen one hour before surgery and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution immediately after approaching the intraperitoneal cavity. Group L (Lidocaine) received an oral placebo one hour before surgery and intraperitoneal instillation of 20 ml of 1% lidocaine immediately after approaching the intraperitoneal cavity. Group IL (Ibuprofen+Lidocaine) received 400 mg of oral ibuprofen one hour before surgery and intraperitoneal instillation of 20 ml of 1% lidocaine immediately after approaching the intraperitoneal cavity. Group P (Placebo) received an oral placebo one hour before surgery and intraperitoneal instillation of 20 ml of isotonic sodium chloride solution immediately after approaching the intraperitoneal cavity. The lidocaine dosage was chosen based on a previous study[12]. Group allocation was performed via computer-generated variable block randomization, and the results were concealed in sealed opaque envelopes. The surgeon, patient, and assistants were all blinded to the randomization sequence. There were no labels to identify the solution or tablet administered.

Participants were advised to practice assessing their pain using a numerical rating scale (NRS, 0 = no pain; 10 = the most severe pain) before the procedure. Non-invasive blood pressure and pulse oximeter

monitoring was employed before, during, and after the procedure. Participants were brought into the operating room one hour after receiving either ibuprofen or a placebo. The trained 2nd year residents infiltrated 10 ml of 1% lidocaine into the skin and behind the rectus sheath of each woman. Numbness was tested prior to making the subumbilical skin incision. After approaching the intraperitoneal cavity, 20 ml of either saline or 1% lidocaine were instilled at both sides of the fallopian tubes (10 ml each). Tubal ligation was performed by a resident using the Pomeroy technique one minute after instillation. Patients received rescue drugs if their pain score was > 5. Research assistants who were blinded to the assigned intervention assessed the severity of pain when tying the second fallopian tube and immediately and one hour after the procedure. Side effects of lidocaine and ibuprofen, such as epigastric discomfort, tinnitus, disorientation, and perioral numbness, were monitored and documented for one hour after surgery.

A sample size of n = 20 per group was required to provide 80% power and alpha 0.05 level comparison to detect meaningful differences in pain intensity (NRS = 2.4)[13]. Assuming a 5% rate of withdrawal, we calculated a final sample size of 23 per group. We performed analyses using SPSS (version 16.0, SPSS Inc., Chicago, IL). Age and BMI were documented, as were duration of surgery, intra-operative pain (while tying the fallopian tube), post-operative pain (immediately and one hour after surgery), rescue medication use (meperidine and diazepam), and adverse effects (e.g., epigastric pain, dizziness, nausea, nor vomiting). Multiple comparisons were conducted using Bonferroni and Dunnet's tests. The p value < 0.05 was considered to be statistically significant. For Bonferroni test, p value < 0.008 was deemed to have statistical significance.

Results

Of 168 postpartum women who were approached, 76 were excluded: 31 who did not meet the inclusion criteria, 39 who declined to participate, three with previous pelvic surgery, and three with BMI ≥ 30 kg/m^2 (Fig. 1). The mean age of participants was 32.6 years. As shown in Table 1, the four groups were comparable in terms of baseline characteristics. However, duration of surgery was slightly longer in Groups I and P.

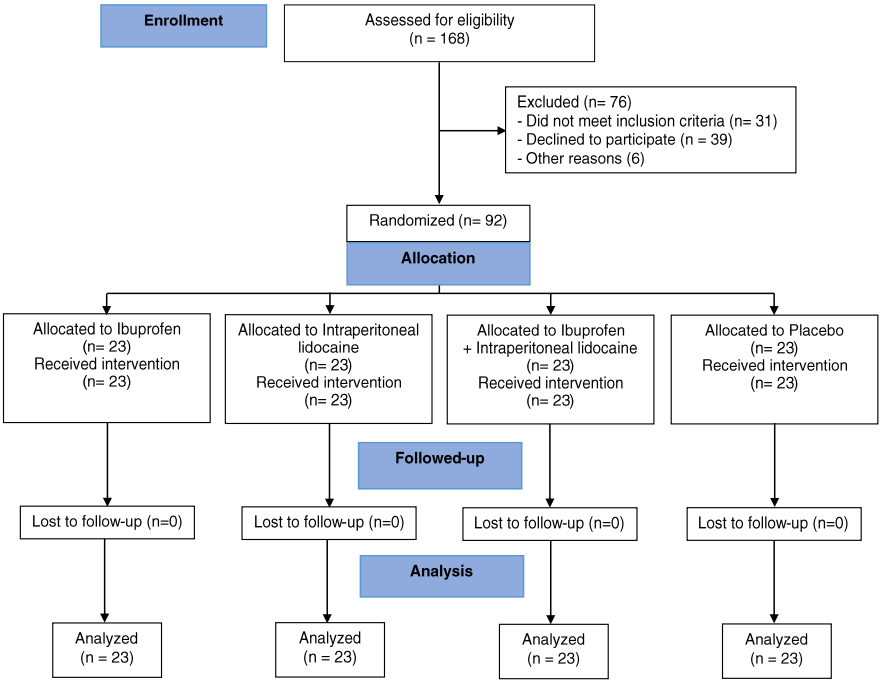

Fig. 1. Flow diagram of the study

Table 1. Demographic data.

Characteristics	Group I (Ibuprofen) n=23	Group L (Intraperitoneal lidocaine) n=23	Group IL (Ibuprofen with Intraperitoneal lidocaine) n=23	Group P (Placebo) n=23
Age (years)	33.4 ± 3.5	33.1 ± 4.6	32.0 ± 3.9	31.8 ± 4.0
Weight (kg)	60.7 ± 7.0	63.7 ± 7.2	66.1 ± 6.5	63.3 ± 8.3
Height (cm)	158.6 ± 4.1	160.5 ± 6.2	159.8 ± 6.1	159.9 ± 5.6
BMI (kg/m^2)	24.2 ± 2.9	24.7 ± 1.8	25.0 ± 3.0	24.7 ± 2.5
Duration of surgery (min)	34.3 ± 16.7	29.9 ± 12.1	30.0 ± 16.7	36.4 ± 14.1

Data presented as mean ± standard deviation
NRS: numerical rating score, BMI: body mass index

Mean NRS was lowest in group IL (3.3 ± 2.6), followed by group L (4.2 ± 2.6). There were no obvious differences in terms of post-operative pain at any time point (Table 2). Preemptive ibuprofen was not effective when compared to placebo (mean difference [MD] 0.70 [95% CI -1.29 to 2.69]), but mean NRS in the IL groups were substantially lower than in the non-lidocaine groups (group I and P; MD -3.17 [95% CI -5.16 to -1.18] and -2.48 [95% CI -4.47 to -0.49], respectively). Effects of lidocaine did not differ significantly from ibuprofen or placebo. No significant differences in postoperative pain were observed (Table 3). The number of paracetamol tablets required did not differ substantially across the four groups.

Although the proportion of patients who required rescue medication were lower in groups L and IL than in group P (Table 4), these differences were not statistically significant (odds ratio (OR) 0.30 95% CI [0.08 to 1.1] and 0.70 [0.22 to 2.26], respectively). Participants reported no adverse effects or serious adverse events during the study period.

Table 2. Intra-operative and post-operative NRS.

Characteristics	Group I (Ibuprofen) n=23	Group L (Intraperitoneal lidocaine) n=23	Group IL (Ibuprofen with Intraperitoneal lidocaine) n=23	Group P (Placebo) n=23
Intraoperative NRS	6.5 ± 2.4	4.2 ± 2.6	3.3 ± 2.6	5.8 ± 2.3
Immediate post-operative NRS	5.6 ± 3.3	5.8 ± 3.0	5.8 ± 2.6	5.5 ± 2.5
1-hour post-operative NRS	2.0 ± 1.9	3.0 ± 1.9	2.4 ± 2.1	3.0 ± 1.9

Data presented as mean ± standard deviation
NRS: Numerical rating score

Table 3. Intra-operative, immediately post-operative, and 1-hour post-operative NRS.

	Mean difference	95% CI	p value
Intraoperative NRS			
Group IL VS Group L	-0.87	-2.86 to 1.12	1.000
Group IL VS Group I	-3.17	-5.16 to -1.18	< 0.001*
Group IL VS Group P	-2.48	-4.47 to -0.49	0.007*
Group L VS Group I	-2.30	-4.29 to -0.31	0.014
Group L VS Group P	-1.61	-3.60 to 0.38	0.190
Group I VS Group P	0.70	-1.29 to 2.69	1.000
Immediate post-operative NRS			
Group IL VS Group L	0.04	-2.23 to 2.31	1.000
Group IL VS Group I	0.26	-2.01 to 2.53	1.000
Group IL VS Group P	0.35	-1.92 to 2.62	1.000
Group L VS Group I	0.22	-2.05 to 2.49	1.000
Group L VS Group P	0.30	-1.97 to 2.58	1.000
Group I VS Group P	0.09	-2.18 to 2.36	1.000
1-hour post-operative NRS			
Group IL VS Group L	-0.52	-2.07 to 1.03	1.000
Group IL VS Group I	0.48	-1.08 to 2.03	1.000
Group IL VS Group P	-0.52	-2.07 to1.03	1.000
Group L VS Group I	1	-0.55 to 2.55	0.513
Group L VS Group P	0	-1.55 to 1.55	1.000
Group I VS Group P	-1	-2.55 to 0.55	0.513

Multiple comparisons were conducted using the Bonferroni test and Dunnet's test.
* Statistical significance ($p < 0.008$)
Group IL: ibuprofen + lidocaine, Group I: ibuprofen, Group L: lidocaine, Group P: placebo, NRS: numerical rating scale, CI: confidence interval

Table 4. Rescue medication requirement during the operation.

Treatment group	Rescue medication required (%)	Unadjusted OR (95% CI)
Group I	12/23 (52.2)	1.19 (0.37 to 3.8)
Group L	5/ 23 (21.7)	0.30 (0.08 to 1.1)
Group IL	9/23 (39.1)	0.70 (0.22 to 2.26)
Group P	11/23 (47.8)	Reference

Multiple comparisons were conducted using the Bonferroni test and Dunnet's test.
* statistical significance ($p < 0.008$)
Group IL: ibuprofen + lidocaine, Group I: ibuprofen, Group L: lidocaine, Group P: placebo, NRS: numerical rating scale, OR: odds ratio, CI: confidence interval

Discussion

We found that ibuprofen with lidocaine instillation was the most effective method of pain relief during PPTL. However, lidocaine instillation or ibuprofen alone did not exhibit similar effectiveness. None of the regimens differed in terms of postoperative pain reduction.

Although preemptive analgesia has long been practiced, in our study, administration of preemptive ibuprofen was inadequate to control pain during PPTL. This was consistent with a previous study, which found that providing morphine one hour preoperatively was not effective at improving intraoperative pain[14]. Furthermore, other studies have found that preemptive NSAID usage in patients undergoing laparoscopic tubal ligation only resulted in a trivial pain reduction[15,16]. A recent systematic review on preoperative NSAID administration also yielded mixed results[17]. This may be explained by the fact that the type of operation and location of pain differed across studies[18]. Although ibuprofen did not have any remarkable effect in our study, further research is needed to evaluate that of other types and dosages of NSAIDs for this procedure. Our results contrasted with those of a study by Visalyaputra et al[14], in which intraperitoneal lidocaine effectively alleviated pain during PPTL. This difference might be due to the lower dosage of lidocaine used in this study. Furthermore, we found that this effect became more pronounced when lidocaine was given in conjunction with preemptive ibuprofen. This is because of the synergistic effect of multiple analgesics, each targeting different receptors of the pain pathway (multimodal analgesia)[19, 20]. The enhanced recovery after surgery (ERAS) recommendations for gynecologic surgery suggest using multimodal analgesia employing multiple agents that address distinct routes to minimize opioid consumption and hasten recovery[21,22]. However, the protocol needs to be adjusted to increase the effect size and extend the effect to cover postoperative pain. Our results showed no difference in postoperative pain, even in the group anesthetized using the multimodal method. This was consistent with previous studies[12,14]. The explanation for this might be that lidocaine and ibuprofen both have a short half-life[23, 24]. Use of a combination of drugs with a longer half-life is worth consideration for future research.

To our knowledge, this is the largest sample size to be enrolled in a double-blind RCT evaluating pain control for PPTL. However, there were limitations pertaining to the subjective nature of pain perception and varying skill level of the residents who performed the operation.

Conclusion

Our study showed that preemptive ibuprofen and intraperitoneal lidocaine instillation alone were not effective at relieving pain in postpartum tubal resection. Multimodal analgesia using both agents was effective for intraoperative (but not postoperative) pain control.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Knowledge, Attitudes, Practices and Mental Health Impact of COVID-19 to Pregnant Women in 2020 and 2021

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ABSTRACT

Objectives: To evaluate and compare the knowledge, attitudes, practices and mental health impact of Coronavirus-19 (COVID-19) on Thai pregnant women between 2020 and 2021 and to identify the factors associated with these outcomes

Materials and Methods: A self-administered questionnaires and Thai General Health Questionnaire-28, (Thai GHQ-28) was given to pregnant women ages 18 and above who attended antenatal care at Songklanagarind Hospital between July-September, 2020 and July-November, 2021. Three hundred and sixty women were recruited in each period. The knowledge, attitudes, practices, mental health status and factors associated with the outcomes were analyzed.

Results: The participants with good knowledge (score 12-15) increased from 27.5% in 2020 to 42.5% in 2021. Factors associated with good knowledge were high education, government or state enterprise employee, high income and survey in 2021. Positive attitudes (≥ 4/5 items) were unchanged between the two periods (65.3% vs 67.5%). Most of the women had good practices (≥ 8/10 items) and these were improved significantly in 2021 (78.9% vs 87.2%). Factors associated with good practices were high education, high income, good knowledge scores and survey in 2021. The COVID-19 outbreak had mild negative impact on mental health. Only 0.83% of participants in 2020 and 3.89% of those in 2021 had Thai GHQ-28 scores ≥ 6 that needed additional psychological support. Factors associated with the mental health problems were marital status, increased severity and numbers of infected cases in 2021.

Conclusion: Knowledge and practices about COVID-19 infection improved from 2020 to 2021. Pregnant women have low incidence of mental health problems.

Keywords: knowledge, attitudes, practices, mental health, COVID-19

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ความรู้ เจตคติ การปฏิบัติตนและผลกระทบต่อสุขภาพจิตของโรคโควิด-19 ต่อสตรีตั้งครรภ์ ช่วงปี พ.ศ. 2563 และ 2564

ปานฝัน วงศ์กิตติถาวร, ฐิติมา สุนทรสัจ, จารุรินทร์ ปิตานุพงศ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อสำรวจและเปรียบเทียบความรู้ เจตคติ การปฏิบัติตนและผลกระทบต่อสุขภาพจิตของโรคโควิด-19 ต่อสตรีตั้งครรภ์ ช่วงปี พ.ศ. 2563 และ 2564 รวมทั้งวิเคราะห์ปัจจัยที่สัมพันธ์กับผลลัพธ์เหล่านี้*

วัสดุและวิธีการ: *ศึกษาในสตรีตั้งครรภ์อายุ 18 ปีขึ้นไปที่มาฝากครรภ์ที่โรงพยาบาลสงขลานครินทร์ช่วงเดือนกรกฎาคมถึงกันยายน พ.ศ. 2563 และช่วงเดือนกรกฎาคมถึงพฤศจิกายน พ.ศ. 2564 จำนวน 360 คนต่อช่วงเวลา โดยใช้แบบสอบถามและแบบประเมินสุขภาพจิต Thai-GHQ 28 ให้ตอบด้วยตนเอง วิเคราะห์ข้อมูลและปัจจัยที่สัมพันธ์กับผลลัพธ์เหล่านี้*

ผลการศึกษา: *สตรีตั้งครรภ์ที่มีความรู้เกี่ยวกับโรคโควิด-19 อยู่ในเกณฑ์ดี (12-15 คะแนน) เพิ่มสูงขึ้นจากร้อยละ 27.5 ในปี พ.ศ. 2563 เป็นร้อยละ 42.5 ในปี พ.ศ. 2564 ปัจจัยที่มีผลต่อคะแนนความรู้ดีคือ การศึกษาสูง อาชีพรับราชการหรือพนักงานรัฐวิสาหกิจ รายได้สูงและการสำรวจช่วงปี พ.ศ. 2564 ทัศนคติเชิงบวก (≥ 4/5 ข้อ) ไม่เปลี่ยนแปลงระหว่างสองช่วงเวลา (ร้อยละ 65.3 ในปี พ.ศ. 2563 และร้อยละ 67.5 ในปี พ.ศ. 2564) สตรีตั้งครรภ์ส่วนใหญ่ปฏิบัติตนดี (≥ 8/10 ข้อ) และเพิ่มขึ้นอย่างมีนัยสำคัญ (ร้อยละ 78.9 ในปี พ.ศ. 2563 เป็นร้อยละ 87.2 ในปี 2564) ปัจจัยที่มีผลต่อการปฏิบัติตนดีคือ การศึกษาสูง รายได้สูง ความรู้ดีและการสำรวจช่วงปี พ.ศ. 2564 ผลของโรคต่อสุขภาพจิตพบน้อย สตรีตั้งครรภ์เพียงร้อยละ 0.83 ในปี พ.ศ. 2563 และร้อยละ 3.89 ในปี พ.ศ. 2564 มีคะแนน Thai GHQ-28 มากกว่าหรือเท่ากับ 6 ซึ่งต้องได้รับการช่วยเหลือและดูแลด้านจิตใจ ปัจจัยที่มีผลกระทบต่อสุขภาพจิตคือ สถานภาพสมรสและการระบาดของโรคที่เพิ่มความรุนแรงและมีผู้ติดเชื้อมากขึ้นในปี พ.ศ. 2564*

สรุป: *ความรู้และการปฏิบัติตนเกี่ยวกับโรคโควิด-19 ดีขึ้นในปี พ.ศ. 2564 ส่วนผลกระทบต่อสุขภาพจิตของสตรีตั้งครรภ์พบน้อย*

คำสำคัญ: *ความรู้, เจตคติ, การปฏิบัติตน, ผลกระทบต่อสุขภาพจิต, โรคโควิด-19*

Introduction

Epidemic infectious disease affects not only physical health but also mental health. Whether it was the severe acute respiratory syndrome (SARS-CoV) outbreak in 2002-2003, the Influenza virus (H1N1 influenza) outbreak in 2009, the Middle East Respiratory Syndrome (MERS-CoV) outbreak in 2012, the Ebola virus outbreak in 2014, or the Coronavirus disease (COVID-19) pandemic in 2019. All of these outbreaks had a significant impact on human mental health globally[1-4]. It affected human life in terms of economic, social and lifestyle changes[5], grief and loss caused by illness and death[6], a terrible experience of dealing with adversity during the outbreak[7,8].

COVID-19 infection first emerged in Wuhan, People's Republic of China in December 2019. Following that, it spread rapidly and has infected millions of people worldwide. On January 30, 2020, COVID-19 was announced as a pandemic public health emergency by the World Health Organization[9]. It is the most serious infectious disease outbreak that has resulted in pneumonia since the SARS outbreak in 2003[10,11]. The COVID-19 outbreak in Thailand began on January 8, 2020. By May 3, 2020, the disease had spread to all provinces across the country which led to 2,969 cumulative patients and 54 deaths. This outbreak has an impact more or less on all human lives in terms of economics, society, and changing lifestyles such as working from home, mandatory wearing of face masks when going outside, washing hands with antiseptic soap or alcohol gel, and social distancing from others as precautionary measures to control the spread of the virus. The government has issued a state of emergency declaring lockdowns in all local regions across the country. Schools, universities, malls, shops, restaurants and entertainment venues have been closed. Restrictions have been put in place on travel outside the province and limiting travel in and out of the country. These led to an economic slowdown, unemployment, lack of income, debt burden causing stress, anxiety, fear and insecurity. Depression and suicide may occur.

The World Health Organization has acknowledged coronavirus disease 2019 (COVID-19) disease as a pandemic. Efforts are being made all over the world to raise awareness to prevent the spread of the disease. In 2020 there were a total of 6,772 patients, with 67 deaths in Thailand. By September 30, 2022, the total number of infected persons worldwide had risen to 631,828,240 cases with 6,545,364 deaths while Thailand had 4,681,309 confirmed cases and 32,764 cumulative deaths. From April 1, 2021 to July 15, 2022, there were 14,601 infected pregnant women and 123 deaths[12].

Pregnant women with COVID-19 infection are more likely to have severe symptoms than non-pregnant women. Severe symptoms include an increased likelihood of being admitted to the intensive care unit (ICU), using a ventilator, and increasing the incidence of premature birth, particularly if the infection occurs during the third trimester[13]. According to Pattanachairuj et al[14], pregnant women with COVID-19 infection were at significantly increased risk of preterm delivery and had a longer hospital stay. However, no significant differences in neonatal outcomes and no vertical transmission were detected in this study. Moreover, a study comparing clinical characteristics and prognostic markers in pregnant women during the first wave (August 1, 2020 to January 31, 2021) and second wave (February 1 to June 30,2021) of COVID-19 in India[15] found that clinical characteristics and disease severity did not differ significantly between the two periods.

Pregnant women are a group that may be affected by COVID-19 in terms of infection concerns and the safety of the unborn baby. Pregnant women in Hong Kong changed their lifestyles to avoid infection during the SARS outbreak, according to Lee et al[16]. Two-thirds of pregnant women were terrified of visiting the hospital. Furthermore, one-third of pregnant women avoided going to the hospital by canceling or postponing antenatal appointments. In addition, it was discovered that pregnant women's stress levels were higher during the outbreak than before. Pregnant

women, for example, are more likely to overestimate their vulnerability to viral infection and to be concerned about infection, such as infection transmission to the unborn child or infection during childbirth. Ng et al[17] found that 82.2 percent of pregnant women were aware of the SARS outbreak's impact on their daily lives which influenced one's mental state, economic and social circumstances. About 27.5% of pregnant women had a moderate level of stress, while 30.2% had a high level. In fact, there is limited information regarding knowledge, attitudes, practices, and mental health impact of COVID-19 to pregnant women in Thailand. Therefore, it is of interest to explore the knowledge, attitude, practices and mental health impact of Thai pregnant women towards COVID-19 disease during the pandemic period and compare these issues between the years of 2020 and 2021. We also evaluated the association between potential influencing factors and these aspects.

Materials and Methods

The study was conducted at antenatal clinic of Songklanagarind Hospital after approval by the Institutional Review Board (code number: REC.63-216-12-4). Pregnant women from the age of 18 and above who are literate in Thai, without psychiatric disorders or emergency conditions were recruited between July-September, 2020 and July-November, 2021. Self-administered questionnaires about knowledge, attitudes and practices were given after informed consent was obtained. The questionnaires were developed, and content validity was assessed by two experienced obstetricians. A pilot study involving 30 pregnant women whose characteristics were matched with inclusion criteria was conducted to test its reliability using Cronbach's alpha statistics. It was calculated as 0.75. Mental health was assessed by Thai General Health Questionnaires-28 (Thai GHQ-28)[18].

The COVID-19 knowledge section included 15 questions (answers: true/false/do not know) about the disease basics, symptoms, and prevention of COVID-19, with 1 point given for each correct answer and 0 point given for an incorrect or "do not know" answer. Total scores were classified as poor (range, 0-6), average (range, 7-11), good (range, 12-15).

The section on attitudes towards COVID-19 consisted of five item. There were four positive attitude items and one negative attitude items with five levels of response: strongly disagree, disagree, neutral, agree, and strongly agree. For positive items, with 1 point given for each "strongly agree" or "agree" and 0 point given for "strongly disagree", "disagree" or "neutral". Whereas negatively interpreted questions were given 1 point for each "strongly disagree", "disagree" and 0 point given for "strongly agree", "agree", or "neutral". Positive attitude was defined as a score of ≥ 4/5.

The practices within the last 7 days evaluated by ten items and classified into four categories: never done, less than 50%, more than 50%, or always done. One point was given for each "more than 50%" or "always done" answer and 0 point was given for each "never done" or "less than 50%" answer. The good practice was defined as a score of ≥ 8/10.

Thai GHQ-28 questionnaires assess four main personality problems: somatic symptoms, anxiety and insomnia symptoms, social dysfunction and severe depression. The scores are calculated in the form (0-0-1-1), which mean that the first two choices have the same value, 0 point each, and the last two choices have the same value, 1 point each. A total score of 6 or higher is considered abnormal. Then, further in-depth interview and evaluation by the first author was done. In case that have severe symptoms, a referral to a psychologist is provided.

The sample size was calculated based on the 30.2% of prevalence of severe mental health impacts of SARS endemic to pregnant women in Hong Kong[17]. The type 1 error ($\alpha = 0.05$) and acceptable of margin at 0.05 were used. At least 324 cases were required. To allow 10% for lost to follow-up, a total of 360 cases were recruited in each period.

The R program version 3.6.2 was used for statistical analysis. Descriptive statistics and multivariate logistic regression were assessed to identify factors associated with good knowledge

scores, positive attitudes, good practices, and mental health status. A p value of < 0.05 was considered statistically significant.

Results

A total of 720 pregnant women were recruited. Demographic and obstetric data are shown in Table 1. Two-thirds were Buddhist (69.3%). The age range was 16-46 years; the average age was 31.4 years. The majority of the women were married (91.8%), in their third trimester (45%), and over 40% were in their first pregnancy, had obtained a bachelor's degree (59.3%), and reported a monthly household income of 10,000-30,000 baht (51.4%), had no underlying disease (81.9%), and had no complications during this pregnancy (74.7%).

Table 1. Demographic data (n = 720).

	n (%)	mean ± SD
Age (years)		**31.35 ± 5.07**
< 20	7 (1.0)	
20 - 34	510 (70.8)	
≥ 35	203 (28.2)	
Religion		
Buddhism	499 (69.3)	
Christianity	4 (0.6)	
Islam	217 (30.1)	
Marital status		
Single	52 (7.2)	
Married	661 (91.8)	
Divorced/Widowed	7 (1.0)	
Parity		
Nulliparity	290 (40.3)	
Multiparity	430 (59.7)	
Education		
High school diploma or equivalent	213 (29.6)	
Bachelor's degree	427 (59.3)	
Master's degree or higher	80 (11.1)	
Occupation		
Housewife/ unemployed	189 (26.3)	
Government or state employee	259 (36.0)	
Employee/ self-employed	258 (35.8)	
Agriculturalists	14 (1.9)	
Monthly household income (baht/month)		
< 10,000	244 (33.9)	
10,001 - 30,000	370 (51.4)	
> 30,000	106 (14.7)	
Gestational age		**24.8 ± 10.3**
First trimester	159 (22.1)	
Second trimester	237 (32.9)	
Third trimester	324 (45.0)	
Complications during this pregnancy		
No	538 74.7)	
Yes	182 (25.3)	
Medical condition (Gestational diabetes mellitus, Pregnancy induced hypertension)	91 (12.6)	
Non-medical condition (Fetal growth restriction, Twin pregnancy, Fetal anomaly, History of threatened abortion or premature uterine contraction)	78 (10.9)	
Others (abnormal placenta, cervical incompetence, proteinuria, ovarian tumor)	13 (1.8)	
Underlying disease		
No	590 (81.9)	
Yes	130 (18.1)	
A history of close contact or family member of COVID-19		
No	715 (99.3)	
Yes	5 (0.7)	

The median knowledge score was 10 out of 15 (range, 4-15). Most women (62.2%) had average knowledge scores (7-11), 35% of participants had good knowledge scores (12-15). Only 2.8% of the participants had poor knowledge scores (0-6). Good knowledge scores increased significantly from 27.5% in 2020 to 42.5% in 2021. In 2020, there were seven items that over 80% of the participants answered correctly and these were eight items in 2021 as shown in Table 2.

Table 2. Knowledge of COVID-19 among participants (n = 720).

Statements	Correct answer	Correct (%) 2020	Correct (%) 2021	p value
1. COVID-19 infection is caused by a virus.	True	98.1	98.3	1
2. Symptoms include fever, cough, sore throat, runny nose, and shortness of breath.	True	99.2	97.5	0.181
3. Most of infected persons have mild symptoms and are self-recovering	True	23.1	26.4	0.578
4. Some patients experience diarrhea.*	True	51.7	79.7	< 0.001
5. Loss of smell is one symptom of COVID-19.*	True	41.7	90.6	< 0.001
6. Mosquito bites can spread the disease.	False	81.9	76.7	0.205
7. Asymptomatic infected persons can spread the disease.	True	92.8	93.9	0.322
8. COVID-19 can be transmitted through food and drink.	True	79.7	78.3	0.133
9. The virus is found in breast milk.	True	21.4	14.7	0.066
10.Pregnant women with COVID-19 are more likely to develop serious illness than general population.*	True	63.6	82.2	< 0.001
11. Children and teenagers are the most likely to die from COVID-19.	False	86.1	86.7	0.967
12. Frequent hand-washing with soap and water can prevent infection.*	True	96.7	92.5	0.021
13. Taking vitamin C can help prevention of disease.*	False	55.8	46.4	0.018
14. Wearing a face mask when going outside can reduce the risk of contracting COVID-19.	True	100	100	1
15. There is a possible risk of fetal anomaly in pregnant women with COVID-19 infection.	False	27.5	34.2	0.063

*Significant, $p < 0.05$

The knowledge items that improved significantly in 2021 were some patients experience diarrhea, loss of smell is one symptom of COVID-19, pregnant women with COVID-19 are more likely to develop serious illness than the general populations. However, two items that participants decreased correct answers were frequent handwashing with soap and water can prevent infection and taking

vitamin C can help prevention of disease. The correct answers with less than 30% were there is a possible risk of fetal anomaly in pregnant women with COVID-19 infection, most of infected persons have mild symptoms and are self-recovering and the virus is found in breast milk.

Details of the questionnaire related to attitudes towards COVID-19 among participants are shown in Table 3. There were 5 items on attitudes. Four positive items were COVID-19 patients have risky behaviors or activities, an infected person must isolate, COVID-19 is a dangerous contagious disease, and travelers from countries with a high incidence of COVID-19 infection should not enter Thailand and one negative item was COVID-19 patients are disgusting. From a total of 720 participants, 86.7% disagreed with the negative attitude item, 75.8% to 95.3% agreed with the four positive items as shown in Table 3. However, the positive attitudes (≥ 4/5 items) were not changed between 2020 and 2021 (65.3% vs 67.5%).

Table 3. Attitudes towards COVID-19 among participants (n = 720).

Statements	Expected Positive answer	Positive attitude* (%) 2020	Positive attitude* (%) 2021	Positive attitude* (%) Total
1. COVID-19 patients are disgusting.	Disagree/ Strongly disagree	84.5	88.9	86.7
2. COVID-19 patients have risky behaviors or activities.	Agree/ Strongly agree	71.1	68.3	69.7
3. COVID-19 patients must isolate.	Agree/ Strongly agree	96.4	94.2	95.3
4. COVID-19 is a dangerous contagious disease.	Agree/ Strongly agree	85.0	83.6	84.3
5. Travelers from countries with a high-incidence of COVID-19 infection should not enter Thailand.	Agree/ Strongly agree	76.9	74.7	75.8

* Positive attitude (≥ 4/5 items)

Concerning practicing during COVID-19 pandemic, the top 3 rankings that participants have done more than 50% in the last 7 days were eat clean and well-cooked food, wearing a face mask when you are outside and washing hands frequently. Compare with 2020, the significant increased practices in 2021 were avoiding crowded places, take a shower and change your clothes immediately when go back home, self-measure body temperature, monitoring COVID-19 symptoms and keeping an eye on news of COVID-19 situation as shown in Table 4. Most of pregnant women had good practices (≥ 8/10 items) and these were improved significantly in 2021 (78.9% vs 87.2%). Factors associated with good knowledge scores were high educational level, government or state enterprise employee, high household monthly income, and surveyed in 2021 while the factors associated with good practices were high educational level, high income, good knowledge score and surveyed in 2021. Complication during pregnancy was only the factor related with positive attitudes (Table 5).

Table 4. Practices during COVID-19 pandemic among participants (n = 720).

Statements	Good practices (%) 2020	Good practices (%) 2021	Good practices (%) Total	p value
1. Wearing a face mask when you are outside.	99.4	100	99.7	0.499
2. Wearing a face shield when you are outside.	25	20	22.4	0.129
3. Avoid crowded places	90.3	98.1	94.2	< 0.001
4. Washing hands frequently	98.9	99.2	99.1	1
5. Eat clean and well-cooked food.	100	100	100	1
6. Going out when necessary.	95	96.1	95.6	0.587
7. Take a shower and change your clothes immediately when go back home	86.4	91.4	88.9	0.044
8. Self-measure body temperature	48.1	57.2	52.6	0.017
9. Monitor COVID-19 symptoms	94.2	98.6	96.4	0.003
10. Keeping an eye on news of COVID-19 situation.	89.4	95.8	92.6	0.002

*Good practices (≥ 8/10 items) (practices frequently; 50-100%)

Table 5. Factors associated with knowledge, attitudes and practices.

Factors	Good knowledge Adjusted OR (95% CI)	Good attitudes Adjusted OR (95% CI)	Good practices Adjusted OR (95% CI)
Educational level			
Bachelor's	2.80 (1.90-4.13)	-	2.18 (1.43-3.33)
Master's & PhD	3.33 (1.91-5.80)	-	-
Occupation			
Government employee	2.91 (1.93-4.38)	-	-
Monthly income (baht/month)			
10,000 - 30,000	2.07 (1.43-2.98)	-	1.66 (1.08-2.53)
≥ 30,000	4.15 (2.55-6.75)	-	-
Years of outbreak			
2021	1.95 (1.43-2.66)	-	1.83 (1.22-2.72)
Complication in pregnancy	-	1.57 (1.08-2.29)	-
Good knowledge scores	-	-	1.91 (1.22-2.99)

OR: odds ratio, CI: confidence interval

COVID-19 outbreak had mild negative impacts on mental health. Only 0.83% of participants in 2020 and 3.89% of those in 2021 had Thai GHQ-28 scores ≥ 6 which needed additional psychological support. Eight of seventeen persons reported suicidal thought but did not attempt. The final diagnosis was

adjustment disorder with and without an anxious mood. Factors associated with the mental health problems were marital status, increased severity and numbers of infected cases in 2021 (Table 6).

Table 6. Factors associated with mental health impact.

Factors	Adjusted OR (95% CI)	p value (< 0.05)
Marital status		
Married	0.14 (0.05-0.44)	< 0.001
Years of COVID-19 outbreak		
Increased severity and numbers of infected cases in 2021	4.82 (1.37-16.9)	0.005

OR: odds ratio, CI: confidence interval

The in-depth interview with those having abnormal scores, we found that during the COVID-19 pandemic in 2020, the stress inducer was based on economic issues such as financial hardship or loss of income due to unemployment, obstetric issues such as a history of previous abortion, history of previous hyperemesis or postpartum blue, as well as personal issues such as being a caregiver, feeling insecure due to divorcement, having a long-distance relationship or a family history of conflict. However, in 2021, the stress inducer was health and immunization difficulties rather than economic issues. In 2021, 10 of 14 pregnant women with abnormal scores denied COVID-19 vaccination during pregnancy due to concerns about the safety of vaccine and the possible harm to the fetus.

A total of 17 persons with abnormal scores took part in an in-depth interview conducted remotely by phone call. The problems were feeling anxious or depressed, emotional disturbance or insomnia, fearful of infection, and stressed, making the future seem uncertain. Moreover, the nationwide lockdown, resulting in a loss of income, a disruption of healthcare services and social interaction, particularly with family and friends, all of which contribute to changes in their daily living and mental health. Eight out of 17 women reported suicidal thoughts but did not attempt. A psychiatrist co-evaluated all those with significant mental health consequences and diagnosed them as having an adjustment disorder with or without anxious mode. We were on the phone for about 30 to 60 minutes each, following-up by retaking the Thai GHQ-28 questionnaire to assess their mental health condition in the coming couple weeks. Five of 17 individuals still had GHQ-28 scores higher than 6, indicating that their mental health needed to be closely monitored. Fortunately, their mental health has restored to normal in one to two months, with no extra psychiatrist sessions required.

Discussion

In Thailand, COVID-19 has increased both number of infected cases and deaths during July to August 2021. There were serious impacts on health, economics, lifestyles and social relations. Pregnant women are one of the high risk groups declared by department of disease control, ministry of public health. Thai government has launched policies to control the disease by laws and regulations announcement, provide knowledge, free vaccination, and medication. Many campaigns are established and well cooperated by both public and private sectors. The knowledge about COVID-19 infection is distributed through multiple media platforms such as newspapers, television, websites, and mobile applications. Main contents are cause, symptoms, transmission routes, prevention methods and practices.

Our study showed that the participants in 2021 have a better knowledge of COVID-19 especially in some aspects. For example, they have known unusual

symptoms, including diarrhea and anosmia, and the more severity of disease in pregnant women. However, some issues were still low correctly answered such as most of infected persons have mild symptoms and are self- recovering; taking vitamin C can help prevention. In addition, they lack the specific knowledge of COVID-19 in pregnancy. For example, Coronavirus is found in breast milk and a possible risk of fetal anomaly. Then, these data are useful for establishing an educational program focusing on improving knowledge about COVID-19 infection. On the contrary, Kunno et al[19] surveyed 150 pregnant women in Bangkok and found the knowledge was good (mean score 9 ± 2.3, max = 13) as well as Sukontrakoon's study[20] that reported 75% of 283 pregnant women had high level of knowledge. However, the difference results are from study population, time of survey, details of questions and definition of good knowledge.

Concerning attitudes, more than half of pregnant women (66.4%) had positive attitudes towards the COVID-19 (≥ 4/5 items). Positive attitudes among participants were not changed between the two periods (65.3% versus 67.5%). Kunno et al[19] revealed the mean score of attitudes was 27 ± 3.9, max = 34. Whereas, Sukontrakoon et al[20] reported mostly neutral to negative thoughts and attitudes about the disease. The attitudes are influenced by past experience, beliefs, culture and religion. They have affected on behavior and actions in various situations. Then, reducing fear or negative attitudes and improving appropriate attitudes should be performed. Regarding practices during COVID-19 pandemic, our study found that the majority of women had good practices (≥ 8/10 items) and these were improved significantly in 2021 (78.9% vs 87.2%). The items that participants practiced very well are eating clean and well-cooked food, wearing a face mask when going outside, washing hands frequently, going out when necessary, monitoring COVID-19 symptoms and avoiding crowded places. All these items are advised by department of disease control. Then, Thai pregnant women have good compliances with the government policy. Our findings are the same as Kunno et al[19] that found mean score of practice was 18 ± 1.9, max = 22 and Sukontrakoon et al[20] that showed 88.3% of participants had good health behaviors.

Factors associated with knowledge, attitudes and practices among pregnant women are different between studies. High education, high income, government or state enterprise employee and surveyed in 2021 were significant associated factors with knowledge found in our study, whereas marital status was significantly factor in Kunno's study[19]. Married participants exhibited a 4.9-fold increase of knowledge scores over unmarried participants ($p = 0.001$). In Sukontrakoon's study[20], education was also related to knowledge and health behaviors. Then, it is important to provide knowledge in less educated pregnant women. For attitudes, Kunno et al[19] found that individuals with at least a bachelor's degree showed a 2.7-fold increase of favorable attitudes about COVID-19 over less education ($p = 0.04$) and those aged 26-30 and 31-35 years showed a 2.5-fold increase in favorable attitudes over those aged 25 years or younger. On the contrary, complication during pregnancy was the only factor related to positive attitudes in our study. High education, high income, and high knowledge score were factors associated with good practices in this study. Moreover, Kunno et al[19] reported persons with at least a bachelor's degree had proper practices than those with less education ($p = 0.04$; OR = 2.285, 95%CI 1.110–6.146), and a higher income was associated with higher practice scores ($p = 0.005$; OR = 4.747, 95%CI 1.588–14.192). The age group of 26–30 years was more closely associated with higher practice scores than ages 25 years and younger (OR = 2.413, 95%CI 0.882–6.602). Additionally, Tasnim et al[21] reported that knowledge of the COVID-19 was the best predictor of attitudes and behaviors. The one with greater levels of education had a positive attitude that was noticeably higher than those with lower levels of education. Moreover, the knowledgeable women displayed positive attitudes toward COVID-19.

Recent cohort and meta-analysis studies in

Canada showed that the prevalence of maternal depression and anxiety increased during the COVID-19 pandemic compared with previous estimates. For the within-person comparisons, depression scores were a mean of 2.30 points (95%CI 1.95–2.65) higher and anxiety scores were a mean of 1.04 points (0.65–1.43) higher at the COVID-19 pandemic timepoint, after controlling for time trends[22]. According to our study, the COVID-19 outbreak had a mild negative impact on the mental health of pregnant women. There were only three participants (0.83%) and 14 participants (3.89%) who had Thai GHQ-28 scores ≥ 6 in 2020 and 2021, respectively. Based on our findings, pregnant women with mental health issues refused COVID-19 vaccination during pregnancy due to concerns about vaccine safety and potential harm to the fetus, which corresponds to Preda et al[23], who discovered that the COVID-19 pandemic caused anxiety in the majority of pregnant women, and the level of anxiety influenced their vaccination decisions. Furthermore from Ding et al[24] the degree of anxiety could be influenced by a person's personality, resiliency, education, family support, satisfaction with the quality of their lives, occupation, and financial situation. Anxiety may be impacted by people's knowledge, attitudes, and practices regarding COVID-19 during this pandemic.

However, recent cohort study in Italy, Flacco et al[25] found that individuals who received one or more doses of COVID-19 vaccines did not show an increased risk of death for any cause, death unrelated to SARS-CoV-2 infection, or any of the selected potentially vaccine-related serious adverse events (PVR-SAEs) requiring hospitalization (myocardial infarction, acute heart failure, cardiac arrest, ischemic or hemorrhagic stroke, coronary artery dissection, aortic or peripheral aneurysm, pulmonary embolism, deep vein thrombosis, and myocarditis, or pericarditis). On the contrary, Sukontrakoon et al[20] reported 76.3% of pregnant women had moderate stress level. The high incidence of mental health problems (82.7%) was also found in Sirikul's[26] study that surveyed in Northern Thailand. They demonstrated that new mothers reported feeling anxious, easily angered or irritable, and depressed. According to our study, participants who were surveyed in the year 2021 was 4.8 times worse for mental health than those in the year 2020. The increasing numbers and severity of infected cases in 2021, particularly among pregnant women had an impact on mental health. On the other hand, married women were 0.14 times less likely to develop mental health problems than unmarried women due to emotional support and stress sharing by husbands.

Finally, the COVID-19 outbreak has been linked to negative mental health issues. To mitigate the psychological impact on pregnant women, it is necessary to provide relevant and reliable information, as well as comprehensive counseling and emotional support.

The strengths of our study were large sample size, comparison of 2 peak periods of infection and using self-administered questionnaires that the participants feel more comfortable to answer. However, the limitations were a cross-sectional study conducted at a single hospital based population which may not refer to general population, selection bias because participants joining the study may have good attitudes or high education. Lastly, Thai GHQ-28 is not specific designed for assessment of mental health problems that caused by COVID-19 infection.

Conclusion

In conclusion, participants had better knowledge about COVID-19 in 2021 than in 2020. Positive attitudes did not change between the two periods. The majority of pregnant women reported engaging in healthy practices and these were improved significantly in 2021. The incidence of mental health problems was low though it was higher in 2021. Several influencing factors related to knowledge, attitudes, practices, and mental health impact of COVID-19 were identified, and the results were particularly helpful for establishing an educational program focusing on reducing misconceptions about COVID-19, enhancing attitudes regarding COVID-19 patient care, promoting preventive

measures, and mitigating the psychological effects of the COVID-19 pandemic on pregnant women.

Acknowledgments

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence of Cervical High-risk Human Papilloma Viral Infection in Pregnant Women at HRH Maha Chakri Sirindhorn Medical Center, Thailand

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ABSTRACT

Objectives: To determine the prevalence of high-risk human papilloma viral (HR-HPV) infection and the factors associated with HR-HPV infection among Thai pregnant women.

Materials and Methods: This cross-sectional study was conducted at the HRH Princess Maha Chakri Sirindhorn Medical Center from May 1, 2022 to January 31, 2023. The data were collected through primary HPV testing, liquid-based cytology (LBC), and a questionnaire.

Results: Overall, 188 pregnant women participated in the study. The mean age was 28.91 years old. The prevalence of HPV infection was 12.7% (24/188), and the two most common types were HPV 52 (6/188, 3.1%) and HPV 16 (5/188, 2.66%). No case of HPV type 18 infection was detected. Abnormal cervical cytology smears were detected in 21 samples (11.17%). The women who had multiple partners had a significantly higher risk of HR-HPV infection compared to the group who had only a single partner ($p < 0.05$).

Conclusion: The prevalence of HR-HPV infection during pregnancy in Thai women was 12.7%. Having multiple partners was found to be the greatest risk factor in this study. Primary HPV testing at a prenatal visit may be an option to improve screening coverage and could be considered in future cervical cancer screening programs.

Keywords: human papillomavirus (HPV), cervical cancer, screening, pregnancy, prevalence.

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การศึกษาความชุกของการติดเชื้อเอชพีวีความเสี่ยงสูงที่ปากมดลูก ในสตรีตั้งครรภ์ที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดา ฯ สยามบรมราชกุมารี

มนัสชัย กุลพรศิริกุล, เอื้อมพร ศรีสนธิ์, วิภาดา เหล่าสุขสถิตย์, ฐานิตรา ตันติเตมิท

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกของการติดเชื้อเอชพีวีความเสี่ยงสูงที่ปากมดลูก และปัจจัยเสี่ยงต่างๆของการติดเชื้อเอชพีวีความเสี่ยงสูง ในสตรีตั้งครรภ์ชาวไทย ที่มาฝากครรภ์ที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี มหาวิทยาลัยศรีนครินทรวิโรฒ*

วัสดุและวิธีการ: *งานวิจัยแบบภาคตัดขวาง เก็บข้อมูลจากสตรีตั้งครรภ์ที่มาฝากครรภ์ที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดา ฯ สยามบรมราชกุมารี มหาวิทยาลัยศรีนครินทรวิโรฒ ตั้งแต่วันที่ 1 พฤษภาคม 2565 ถึง 31 มกราคม 2566 โดยการตรวจคัดกรองมะเร็งปากมดลูกด้วยวิธีการตรวจหาเชื้อไวรัสเอชพีวีชนิดความเสี่ยงสูง (Primary HPV testing), การตรวจด้วยวิธีทางเซลล์วิทยาชนิด liquid-based cytology และการตอบแบบสอบถาม*

ผลการศึกษา: *มีสตรีตั้งครรภ์เข้าร่วมการศึกษา 188 ราย อายุเฉลี่ย 28.91 ปี พบความชุกของการติดเชื้อไวรัสเอชพีวีชนิดความเสี่ยงท่ากับ ร้อยละ 12.7 (24/188) เชื้อไวรัสสองชนิดที่พบมากที่สุดคือเอชพีวี 52 (6/188, ร้อยละ 3.1) และเอชพีวี 16 (5/188, ร้อยละ 2.66) การศึกษาครั้งนี้ไม่พบการติดเชื้อเอชพีวี 18 สำหรับการตรวจทางเซลล์วิทยาพบความผิดปกติทั้งหมด 21ราย (ร้อยละ11.17) นอกจากนี้ยังพบว่าการมีประวัติมีคู่นอนหลายคน สัมพันธ์กับการติดเชื้อไวรัสเอชพีวีชนิดความเสี่ยงสูง อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับการมีคู่นอนคนเดียว ($p < 0.05$)*

สรุป: *ความชุกของการติดเชื้อเอชพีวีความเสี่ยงสูงในสตรีไทยที่ตั้งครรภ์พบร้อยละ 12.7 และประวัติการมีคู่นอนหลายคนมีความสัมพันธ์กับการติดเชื้อเอชพีวีชนิดความเสี่ยงสูงในสตรีตั้งครรภ์ การตรวจหาเชื้อไวรัสเอชพีวีในระหว่างฝากครรภ์ทำให้การตรวจคัดกรองมะเร็งปากมดลูกมีความครอบคลุมมากขึ้น และอาจจะพิจารณาเป็นทางเลือกหนึ่งสำหรับแนวทางการป้องกันมะเร็งปากมดลูกในอนาคต*

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Introduction

Cervical cancer is the primary cause of cancer-related deaths among women in low- to middle-income countries. It is the second most common cancer with a mortality rate of 7.4 per 100,000 among women in Thailand[1]. Although it is preventable through proper screening, two-thirds of women aged 30–49 have never undergone screening for cervical cancer[2]. Approximately 50% of Thai women have not taken part in a screening program for cervical cancer[3]. Infection with high-risk human papillomavirus (HR-HPV) plays an important role in the development of cervical cancer[4]. Several studies have reported that primary human papillomavirus (HPV) testing has higher sensitivity than cytology-based methods and could be expected to improve the detection rate of high-grade cervical lesions[4-6]. This method is considered the primary screening option in Thai women aged 30–65 years old.

In 2020, the mean age of childbearing women in Thailand was 27.3 years old, with a high incidence of cervical precancerous lesions[7]. As pregnant women usually adhere to medical follow-up, cervical cancer screening during the antenatal period represents an interesting option to target young women who do not attend regular screening programs and is thus recommended in many developed countries. Some health facilities in Thailand perform cervical cancer screening during pregnancy, but most of them rely on cytologic testing, which often involves difficult evaluations due to hormone-induced changes in the cervix[8]. Therefore, most clinicians prefer to do a Pap smear at 6 weeks postpartum[9]. From a survey of our center, less than 50% of women do not attend a postpartum visit. There have been no studies on primary HPV testing among pregnant women in Thailand yet. However, a previous study reported that abnormal cervical cytology results were found in approximately 4%–7% of Thai pregnant women[10, 11]. Studies from other countries have reported high-risk HPV prevalent rates among pregnant women ranging from 13%–20%[12-14]. Many factors could increase the risk of HPV infection during pregnancy, for example, young age, the number of lifetime sexual partners, and the presence of abnormal cervical cytology[13, 15]. This study aimed to determine the prevalence and factors associated with high-risk human papilloma viral infection among Thai pregnant women in order to assess the feasibility of including a primary HPV screening program during antenatal care.

Materials and Methods

This cross-sectional study was conducted at the HRH Princess Maha Chakri Sirindhorn Medical Center between May 1, 2022, and January 31, 2023. The participants were pregnant women who visited the antenatal care clinic before 28 weeks of gestational age. The inclusion criteria were pregnant women aged over 20 years old, who had an intrauterine pregnancy confirmed by ultrasound. The exclusion criteria were pregnant women who had been screened for cervical cancer within the past year; had a history of abnormal cervical cancer screening, precancerous, or cancerous of cervix; had experienced abnormal vaginal bleeding; who were unable to be on dorsal lithotomy; or who did not understand the Thai language.

The sample size was calculated based on a prevalence of HPV infection in pregnancy of 13.4% from a pilot study. After calculation, a total of 188 participants were included in the study, including cover for a 5% loss. This study was approved by the Ethics Committee of Srinakharinwirot University (SWUEC/E/M-012/2565).

After obtaining informed consent, the participants were asked to complete a questionnaire about their demographics, pregnancy history, cervical cancer screening history, HPV vaccine history, and risk factors for cervical cancer. Cervical cancer screening was conducted using both primary HPV testing and liquid-based cytology (LBC). Specimens were collected from the ectocervix using a Cytobrush in 5 rounds and were stirred into a transport medium solution (Cellprep®, Seongnam, Korea). All the specimens were sent to the Virology Department for

primary HPV testing and then forwarded to the Pathology Department for a single pathologist to report the cytology results according to the Bethesda 2001 reporting system. The HPV results were blinded to the clinical status and cytologic results. HPV testing was performed using a high-risk HPV deoxyribonucleic acid (DNA) diagnostic kit for identification of the HPV genotypes (Sansure Biotech Inc, Hunan, China). This diagnostic kit is an in vitro nucleic acid amplification test for the detection of high-risk human papillomavirus (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68) present in exfoliated cells from a female cervix. The test results can be used for the diagnosis of a high-risk HPV infection. The participants who had HPV type 16 or 18 infection and other high-risk HPV infections with an abnormal cervical cytology (atypical squamous cells of undetermined significance (ASC-US) or more) were referred to a gynecologic oncologist for colposcopic examination.

The patients' demographic data, obstetric profile, history of cervical cancer screening, and risk of cervical cancer were obtained using a questionnaire. Descriptive statistics were used to describe various characteristics, and reported as the mean, frequency, percentage, and standard deviation. The chi-square test was performed to analyze associations between the demographic data and HPV prevalence. The p value was set at 0.05 for statistical significance. All the data were analyzed using Stata version 14.1 For Mac.

Results

Overall, 188 pregnant women were enrolled in this study. The demographic characteristics of these are presented in Table 1.

Twenty-four pregnant women were infected with HR-HPV, representing a prevalence of 12.7% of all pregnant women (Table 2). The two most common types were HPV 52 (6 cases, 3.1%) and HPV 16 (5 cases, 2.6%). Two cases had multiple HPV infections, which were HPV 51, 53, 68, and 52, 53. No case of HPV type 18 infection was detected in this study.

Table 1. Demographic characteristics of the study population (n = 188).

Characteristics	Number (%), mean ± SD
Age (mean ± SD)	28.91 ± 4.95
20 – 29	116 (61.7%)
30 – 41	72 (38.3%)
Gravidity	
Nulliparous	69 (36.7%)
Multiparous	119 (63.3%)
Gestational age at examination (weeks)	12.29 ± 4.15
1st trimester (< 14 weeks)	117 (62.23%)
2nd trimester (≥ 14 weeks)	71 (37.77%)
Education	
< Bachelor's degree	111(59.04%)
≥ Bachelor's degree	77(40.96%)
Income per month (THB)	25,440.43 ± 14794.97
< 20,000	67 (35.64%)
≥ 20,000	121 (64.46%)
History of cervical cancer screening	
No	89 (47.34%)
Yes	99 (52.66%)
History of contraception	
No	65 (34.57%)
Yes	123 (65.43%)
Age at first intercourse (mean ± SD)	19.62 ± 3.82
< 20	96 (51.06%)
≥ 20	92 (48.94%)
Number of partners (mean ± SD)	1.69 ± 0.955
1	106 (56.38%)
≥ 2	82 (43.62%)
History of smoking	
No	186 (98.94%)
Yes	2 (1.06%)
History of HPV vaccine	
No	188 (100%)
Yes	0 (0%)

SD: standard deviation, THB: Thai baht, HPV: Human papillomavirus

Table 2. Prevalence of HPV infection.

HPV types	Number	%
Positive HPV 16	5	2.6
Positive HPV 18	0	0
Other high-risk types	19	10.1
31	2	
39	3	
45	1	
51	1	
52	5	
53	1	
56	1	
58	1	
59	1	
66	1	
52, 53	1	
51, 53, 68	1	
Total	24	12.7

HPV: Human papillomavirus

The results from the liquid-based cytology (LBC) tests and the relationship to HPV status are shown in Table 3. Abnormal cervical cytology smears were detected in 21 samples (11.17%), consisting of 16 (8.5%) with atypical squamous cells of undetermined significance (ASC-US) and five (2.6%) with a low-grade squamous intraepithelial lesion (LSIL). Most of the cases with abnormal cytology were associated with high-risk HPV infection (85.7%). Twenty-five percent of the participants with high-risk HPV infection had normal cervical cytology (6 cases). Twenty cases were referred for colposcopic examination, while only one case was suspected of a high-grade lesion and a cervical biopsy was done during pregnancy. The final pathology of that latter case reported cervical intraepithelial neoplasia 1 (CIN1).

Table 3. Results of cervical cytology in relation to HPV status.

LBC	High-risk HPV infection			
	Undetected	Type 16	Other HR	Total
NILM	161	2	4	167
ASC-US	3	2	11	16
LSIL	0	1	4	5
HSIL	0	0	0	0

LBC: liquid based cytology, HR: high risk, HPV: human papillomavirus.

Table 4 presents a comparison of the patients' characteristics and risk factors of cervical cancer between pregnant women without high-risk HPV infection and those with high-risk

HPV infection. We found that having multiple partners was the only factor associated with an increased risk of HR-HPV infection during pregnancy (p-value < 0.05).

Table 4. Comparison of the characteristics between pregnant women without high-risk HPV infection and with high-risk HPV infection.

Characteristics	Number (%)	No HR-HPV infection	HR-HPV infection	p value
Age				0.592
20 – 29	116 (61.7%)	100 (60.98%)	16 (66.67%)	
30 – 41	72 (38.3%)	64(39.02%)	8 (33.33%)	
Gravidity				0.589
Nulliparous	69 (36.7%)	59 (35.98%)	10 (41.67%)	
Multiparous	119 (63.3%)	105 (64.02%)	14 (58.33%)	
Gestational age at examination (weeks)				0.076
14 weeks	117 (62.23%)	106 (64.63%)	11 (45.83%)	
≥ 14 weeks	71(37.77%)	58 (35.37%)	13 (54.17%)	
Education				0.159
< Bachelor's degree	111(59.04%)	100 (60.98)	11 (45.83%)	
≥ Bachelor's degree	77(40.96%)	64 (39.02%)	13 (54.17%)	
Income per month (THB)				0.478
< 20,000	67 (35.64%)	60 (36.59%)	7 (29.17%)	
≥ 20,000	121 (64.46%)	104 (63.41%)	17 (70.83%)	
History of cervical cancer screening				0.248
No	89 (47.34%)	75 (45.73%)	14 (58.33%)	
Yes	99 (52.66%)	89 (54.27%)	10 (41.67%)	
History of contraception				0.551
No	65 (34.57%)	58 (35.37%)	7 (29.17%)	
Yes	123 (65.43%)	106 (64.63%)	17 (70.83%)	
Age at first intercourse				0.446
< 20	96 (51.06%)	82 (50.0%)	14 (58.33%)	
≥ 20	92 (48.94%)	82 (50.0%)	10 (41.67%)	
Number of partners				0.015
1	106 (56.38%)	98 (59.76%)	8 (33.33%)	
≥ 2	82 (43.62%)	66 (40.24%)	16 (66.67%)	
History of smoking				1.000
No	186 (98.94%)	162 (98.78%)	24 (100%)	
Yes	2 (1.06%)	2 (1.22%)	0 (0.0%)	
History of HPV vaccine				1.000
No	188 (100%)	164 (100.0)	24 (100.0)	
Yes	0 (0%)	0	0	

HR: high risk, HPV: human papillomavirus, THB: Thai baht

Discussion

This study found that the prevalence of HR-HPV-infected pregnant women was 12.7% in our cohort, while the prevalence from previous studies in other countries varied from 13%–20%[12-14]. One study from India collected samples from condoms used to cover the vaginal sonography probe during patients' first-trimester visits, and found a prevalence of almost 40%, which was much higher than in our study[16]. A study from Lithuania reported a prevalence of HR-HPV infection in pregnancy of 9.3%, which was obtained by collecting cervicofacial washing fluid during pelvic examinations in the first and third trimesters[17]. Another study from France collected samples from pregnant women with a gestational age of less than 24 weeks by routine Pap smear and HPV testing and found an HR-HPV prevalence of 20%[14]. The difference in prevalence in various studies could possibly be explained by the differences in the geographical area, HPV detection assay used, sample collection method, and timing of sample collection. The differences in HR-HPV infection rates during pregnancy have also been studied and it was found that the prevalence of HPV infection in the first trimester tends to be higher than in the second trimester[13,18]. With respect to the HR-HPV genotypes, the most common genotype was HPV 52 followed by HPV16. This finding was consistent with a previous study from a large cohort of the general population in Thailand[19]. However, there were no cases in our study infected with HPV18, which is the second most common type worldwide[20]. The low prevalence of this genotype has also been reported in previous Thai studies[19, 21, 22].

The prevalence of abnormal cytological smears in pregnant women in our study was 11.7%, which is higher than in the past studies in Thailand (4%–7%)[10, 11]. The sociodemographic characteristics of the pregnant women in those earlier studies were similar to those in our study. This suggests that the rate of abnormal cytology and preinvasive cervical cancer seems to be increasing. Prenatal care provides an opportune time for screening. Another explanation for the difference in the prevalence of cervical smears among these studies could be the poor reproducibility and limited accuracy of cytological diagnoses[23, 24]. One study conducted in a general Thai population reported that agreement between skilled observers, at the level of tests requiring diagnostic follow-up or not, was only moderate. The discrepancies were greatest for the minor degrees of cytological abnormality in the Bethesda classification[24]. The interpretation of cytologic specimens is more difficult in pregnancy, as the hormonal changes, Aris–Stella reaction, and decidualization in pregnancy result in changes in epithelial cells that simulate malignancy and may cause confusion[8]. For this reason, we recommend HR-HPV testing as the preferred approach in pregnant women.

We found that women with multiple partners had a significantly increased risk of HR-HPV infection in pregnancy. A previous meta-analysis suggested that young pregnant women, especially those aged < 25 years old, were more susceptible to HPV infection[13]. Our study analyzed the prevalence of HPV in different age groups. However, these results need to be verified by further study.

Recently in our country, there has been a movement toward the implementation of HPV testing to precede cytology-based screening programs. It is thus interesting to study HPV-based screening in the target population during pregnancy. To the best of our knowledge, this is the first prospective study in Thailand to report the prevalence of HPV infection during pregnancy. We also reported the prevalence of cervical cytology and the factors associated with HPV infection. The limitations of this study included our small sample size and the fact that only one-time testing was performed in the first half of pregnancy, and we did not repeat HPV testing before delivery or at the postpartum visit to assess HPV clearance. The changes of HPV infection in each trimester and at the postpartum visit have, however, been reported in several studies[13, 17, 18]. Moreover, as a result of the small number of HPV-positive women in our study,

we could not evaluate the association between maternal HPV infection and adverse pregnancy outcomes. Also, due to time constraints and as it was considered beyond the scope of the study, the results of follow-up and adherence to the screening program could not be reported. The clearance of HPV infection, maternal outcome, adherence, and cost-effectiveness of this strategy in pregnancy would be interesting to determine and might be more meaningful to study in the future.

Conclusion

In conclusion, the prevalence of HR-HPV infection during pregnancy in Thai women in our study was 12.7%. The most significant risk associated with having multiple partners was the increased risk of this infection. Our findings suggest that including primary HPV testing in a prenatal visit may be an option to improve screening coverage in Thailand.

Acknowledgments

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Prevalence of Depression and Associated Factors in Postmenopausal Thai Women during the COVID-19 Pandemic

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ABSTRACT

Objectives: To determine the prevalence of and factors associated with depression in postmenopausal Thai women during the COVID-19 pandemic.

Materials and Methods: The study was conducted from April to December 2022. Depression was diagnosed using the Thai Depression Inventory. Self-questionnaires assessed sociodemographic data; COVID-19 knowledge, attitudes, and preventive practices; and Thai Depression Inventory scores.

Results: The study assessed 271 women (175 natural postmenopausal; 96 surgical postmenopausal). The depression prevalence was 9.6% overall, 8.6% in natural menopause, and 11.5% in surgical menopause. No severe major depression was observed. The prevalence of mild depression was significantly higher in the surgical postmenopausal group (11.5%) than in the natural postmenopausal group (4.0%, p = 0.022). In the natural postmenopausal group, the prevalence of less than major depression and major depression were 4% and 0.6%, respectively, whereas it was not present in the surgical postmenopausal group. Women with superior knowledge or attitudes had a lower prevalence. Those with high levels of preventive behavior had a higher prevalence but without significance. Prevalence significantly increased with low household income and medical disease, especially chronic kidney disease.

Conclusion: The prevalence of depression in postmenopausal Thai women during COVID-19 was 9.6%. Low household income and chronic kidney disease were significant predictors.

Keywords: COVID-19, depression, natural menopause, surgical menopause, chronic kidney disease.

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ความชุกและปัจจัยที่เกี่ยวข้องของภาวะซึมเศร้าในสตรีไทยวัยหมดระดูในช่วงการแพร่ระบาดโรคติดเชื้อโคโรนาสายพันธุ์ใหม่ 2019

ณัฐสุดา พันธ์บุญมี, สุชาดา อินทวิวัฒน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อสำรวจความชุกการเกิดภาวะซึมเศร้าในสตรีวัยหมดระดูในช่วงการแพร่ระบาดโรคติดเชื้อไวรัสโคโรนา 2019*

วัสดุและวิธีการ: *ผู้ที่มารับการรักษาในคลินิกต่อมไร้ท่อสตรีและวัยทองโรงพยาบาลศิริราชและมีคุณสมบัติเข้าเกณฑ์ จำนวน 271 คน ทำแบบสอบถามด้วยตนเอง แบบสอบถามประกอบด้วย 3 ส่วน ได้แก่ ข้อมูลพื้นฐาน ความรู้ ทัศนคติ และพฤติกรรมการป้องกันตนเองจากการติดเชื้อไวรัสโควิท-19 จำนวน 16 ข้อ และ แบบสอบถามเพื่อประเมินความรุนแรงของภาวะซึมเศร้าชนิดให้ผู้ป่วยตอบแบบสอบถามเอง จำนวน 20 ข้อ จากนั้นทำการหาความชุกของการเกิดภาวะซึมเศร้าของสตรีวัยหมดประจำเดือน เปรียบเทียบความชุกของภาวะซึมเศร้าในสตรีหมดระดูตามธรรมชาติ และสตรีที่หมดระดูเนื่องจากได้รับการผ่าตัดรังไข่ออกทั้งสองข้าง และหาปัจจัยต่างๆ ที่เกี่ยวข้อง*

ผลการศึกษา: *ความชุกของการเกิดภาวะซึมเศร้าในสตรีวัยหมดระดูในช่วงการแพร่ระบาดโรคติดเชื้อไวรัสโคโรนา 2019 ร้อยละ 9.6 โดยในสตรีหมดระดูตามธรรมชาติร้อยละ 8.6 และร้อยละ 11.5 ในสตรีที่หมดระดูเนื่องจากได้รับการผ่าตัดรังไข่ออกทั้งสองข้าง ทั้งหมดไม่มีภาวะซึมเศร้าแบบรุนแรง เมื่อเปรียบเทียบ ภาวะซึมเศร้าแบบไม่รุนแรงพบความชุกมากกว่าในสตรีที่หมดระดูเนื่องจากได้รับการผ่าตัดรังไข่ออกทั้งสองข้าง (ร้อยละ 11.5) เมื่อเทียบกับสตรีหมดระดูตามธรรมชาติ (ร้อยละ 4.0, p = 0.022) อย่างมีนัยสำคัญทางสถิติ พบภาวะซึมเศร้าแบบปานกลางและแบบรุนแรงในสตรีหมดระดูตามธรรมชาติร้อยละ 4 และร้อยละ 0.6 ตามลำดับ ซึ่งไม่พบในสตรีที่หมดระดูเนื่องจากได้รับการผ่าตัดรังไข่ออกทั้งสองข้าง ผู้ที่มีความรู้ และทัศนคติเกี่ยวกับโรคติดเชื้อไวรัสโควิด-19 ดีกว่า มีความชุกของการเกิดภาวะซึมเศร้าน้อยกว่า และผู้ที่มีพฤติกรรมพฤติกรรมการป้องกันตนเองจากการติดเชื้อไวรัสโควิด-19 ดีกว่า มีความชุกของภาวะซึมเศร้ามากกว่า แต่ไม่มีนัยสำคัญทางสถิติ ปัจจัยที่มีความสำคัญทางสถิติที่เกี่ยวข้องกับการเกิดภาวะซึมเศร้าคือ การที่มีรายได้ในครัวเรือนน้อย การมีโรคประจำตัวโดยเฉพาะอย่างยิ่ง โรคไตเรื้อรัง*

สรุป: *ความชุกการเกิดภาวะซึมเศร้าในสตรีวัยหมดระดูในช่วงการแพร่ระบาดโรคติดเชื้อไวรัสโคโรนา 2019 ร้อยละ 9.6 รายได้ในครัวเรือน และการเป็นโรคไตเรื้อรังเป็นปัจจัยที่เกี่ยวข้องกับการเกิดภาวะซึมเศร้า*

คำสำคัญ: *โรคติดเชื้อไวรัสโคโรนา 2019, ภาวะซึมเศร้า, สตรีหมดระดูตามธรรมชาติ, สตรีที่หมดระดูเนื่องจากได้รับการผ่าตัดรังไข่ออกทั้งสองข้าง*

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a member of the Orthocoronavirinae subfamily, which includes positive single-stranded ribonucleic acid (RNA) viruses. The natural origin and reservoir of the virus are still unknown. The virus spreads through respiratory droplets and aerosols and can cause symptoms ranging from asymptomatic to severe pneumonia and death[1, 2]. Elderly individuals are particularly susceptible to severe clinical outcomes from SARS-CoV-2 infections[3].

SARS-CoV-2 infection was confirmed as the cause of COVID-19 in Wuhan, China, in December 2019. The disease quickly spread worldwide, and the World Health Organization (WHO) declared a pandemic in March 2020. Thailand's first COVID-19 case was detected on January 13, 2020, leading to a government-issued emergency decree on March 26, 2020. The decree included a 'stay home' policy, the cancellation of national holidays, school closures, restricted access to public areas, face mask requirements, and social distancing measures[4]. We hypothesized that COVID-19 might significantly affect people's lives, causing stress due to sudden changes in plans and health concerns. During the early phase of the epidemic in China, the reported rate of depression in the general population was 16.5%, with female sex, student status, chronic illness, and poor health status linked to higher levels of stress, anxiety, and depression[5].

Depression is characterized by at least 2 weeks of persistent sadness, loss of interest, and inability to perform daily activities. The condition can affect job, school, and family performance. In Thailand, 1.5 million people suffer from depression, with 2.4% experiencing major depressive episodes[6]. Although several studies have suggested an association between women and depression during the COVID-19 pandemic, the results have been inconclusive, as demonstrated in Table 1. Most of these studies investigated a wide range of ages and did not specifically focus on women in the menopausal stage[7-10]. Depression is more common among females than males, and the prevalence increases with age[6, 11]. The menopausal transition, a hypoestrogenic stage, is a stressful event. It can lead to depression due to a decline in estrogen levels, which negatively impacts the metabolism of neurotransmitters such as dopamine, norepinephrine, β-endorphin, and serotonin. Menopausal symptoms such as hot flashes, sleep disturbances, and sexual dysfunction are associated with decreased estrogen levels. Risk factors for depression include medical disease and employment, marital and economic issues[12, 13]. We hypothesized that COVID-19-related stress could exacerbate depression prevalence in postmenopausal women with these risk factors. Early detection and treatment of depression can improve the quality of life of affected individuals.

Currently, there is a lack of research examining the prevalence of depression among postmenopausal Thai women during the COVID-19 pandemic. Therefore, this study aimed to investigate the prevalence and related factors of depression in postmenopausal Thai women during the pandemic. Our results could provide valuable insights for diagnosing, treating, and preventing depression in this population.

Table 1. Summary of cross-sectional studies surveying women with depression and its components during COVID-19 pandemic.

Authors	Year of study	Age (yr)	Diagnostic criteria for depression	Sample size	Country	Depression prevalence	Result of depression factors
Kullak-Bejda et al, 2022	2006 vs. 2021.	At least 40	Three questionnaires: 1. The menopause rating scale (MRS) 2. The Blatt–Kupperman menopausal index (BKMI) 3. The Beck depression inventory (BDI)	Menopausal women 2006 (N=241) vs. 2021 (N=350)	Poland	Mild depression: - 36.3% in 2006 - 59.3% in 2021 Moderate depression: - 36.3% in 2006 - 59.3% in 2021 Severe depression: - 3.0% in 2006 - 5.2% in 2021	Menopausal complaints, as evaluated by the BKMI and MRS; increase in depressive moods.
Khatak et al, 2022	May–June 2021	40-60	Four questionnaires: 1. Background Information and Fear of COVID-19 Scale 2. Patient Health Questionnaire (PHQ-9) 3. Generalized anxiety disorder 7 (GAD-7) 4. EuroQol-5D (mobility, self-care, usual activities pain/discomfort and anxiety/depression)	200 menopausal women	India	Minimal depression: 61% Mild depression: 38.5% Moderate depression: 0.5%	Infection; being afraid of losing life; become nervous or anxious while watching COVID-19 news on social media; sleeplessness; and restlessness
Afshari et al, 2022	August–December 2021	-	Three questionnaires: 1. A demographic questionnaire 2. COVID-19 infection information 3. DASS-21(level of depression, anxiety, and stress)	190 infertile women	Iran	Half of the women reported moderate and severe depression and anxiety	Lower in women with good and moderate economic statuses
Cybulska et al, 2022	August–October 2021	41–75	4 questionnaires 1. Beck Depression Inventory (BDI) 2. Spielberg State-Trait Anxiety Scale (STAI: assesses both trait and state anxiety) 3. Blatt–Kupperman Index (BKMI: evaluates climacteric symptoms) 4. Inventory of Social Supportive Behaviors (ISSB)	295 menopausal women	Poland	Mild depression: 13.8% Moderate depression: 7.3% Severe depression: 3.7%	Sociodemographic and medical variables had no significant effects on depression.

Materials and Methods

The study adhered to the ethical principles of the Declaration of Helsinki, and its protocol was authorized by the Siriraj Institutional Review Board (approval number 1039/2564–IRB4). This cross-sectional study recruited postmenopausal women who visited the Gynecologic Endocrinology Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital.

Study population and data collection

This study included postmenopausal women aged at least 40 who attended the Gynecologic Endocrinology Clinic between April and December 2022. Patients with mental disorders, individuals taking antidepressants, or those with incomplete data for depression evaluation were excluded. All participants provided signed informed consent. Self-reported data consisted of 3 main sections: sociodemographic information; knowledge, attitudes, and preventive practices (KAPs) related to COVID-19; and the Thai Depression Inventory questionnaire.

The sociodemographic data collected in this study comprised age, age at menopause, menopausal status, marital status, parity, education, occupation, household income, postmenopausal hormone therapy, medical history of metabolic diseases (diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease), COVID-19 vaccination status, and previous COVID-19 infection in the family. Physical examinations were performed to measure the participants' height (in cm) and weight (in kg), and body mass index was calculated.

Definitions of menopausal status

The study participants were categorized into 2 groups based on their menopausal status: natural postmenopausal women and surgical postmenopausal women. Natural postmenopausal women were defined as those who had experienced 12 consecutive months of amenorrhea or had follicle-stimulating hormone levels over 40 IU/L without any apparent pathological or physiological causes for amenorrhea. Surgical postmenopausal women were defined as those who had undergone surgical removal of both ovaries, with or without hysterectomy[14].

KAPs related to COVID-19

To evaluate public awareness of COVID-19, it is necessary to assess the KAPs related to the disease. The COVID-19 KAP questionnaire developed by Zhong et al in 2020[15] was translated into Thai by Khumsaen in 2021[16], and it was found to have a Cronbach's alpha score of 0.81. The COVID-19 KAP questionnaire has 16 questions related to COVID-19. Twelve of the questions assess knowledge, 2 questions evaluate attitudes, and 2 questions examine COVID-19-related practices. Participants were asked to answer with 'true,' 'false,' or 'unsure' responses.

The rating scale for the 12 knowledge questions is divided into 3 levels. Low scores range from 0.00 to 4.00, moderate scores span from 4.01 to 8.00, and high scores extend from 8.01 to 12.00. In the case of the 2 attitude questions, participants are given 1 point for answering 'true' and zero points for answering 'false' or 'unsure.' The rating scale for attitudes has 2 levels: low scores range from 0.00 to 1.00, and high scores range from 1.01 to 2.00. Regarding the 2 preventive practices questions, participants are asked about their habits of going to crowded locations and using a mask. Participants receive 1 point for answering 'false' and zero points for answering 'true' or 'unsure.' The rating scale for preventive practices also has 2 levels, with low scores ranging from 0.00 to 1.00 and high scores ranging from 1.01 to 2.00.

Criteria for the diagnosis of depression

In 1999, Lotrakul et al developed a self-rating instrument called the Thai Depression Inventory to measure the severity of depression[17]. It was published in the Journal of the Psychiatrist Association of Thailand. The instrument comprises 20 questions divided into 6 factors: anxiety syndrome, depression factor, hypochondriacal factor, somatic symptoms of anxiety, somatic symptoms of depression, and psychomotor retardation. Each item is scored on a

scale of 0 to 3, with a maximum total score of 60. Total scores are classified into 5 groups: no depression (≤ 20), mild depression (21–25), less than major depression (26–34), major depression (35–40), and severe major depression (≥ 40). The gold standard used to evaluate the Thai Depression Inventory was the Hamilton Depression Rating Scale, and the instrument was found to have a Cronbach's alpha score of 0.86.

Statistical analysis

The sample size for this study was calculated using the formula for descriptive studies, and the sampling method was convenience sampling. An investigation by Wang and colleagues in 2020 reported that the prevalence of depression among the general population in China during the early phase of the COVID-19 outbreak was 16.5%[5]. However, earlier research indicated that the prevalence was higher among elderly and female individuals[11]. Therefore, we hypothesized a prevalence of 20% among menopausal women, with a precision error of estimation (d) of 0.05 (or 5% of P), alpha of 0.05, and a margin of error of 10%. The required sample size for prevalence estimation was at least 271 cases.

The data were analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as the mean ± standard deviation, number (%), or percentage (95% CI), as appropriate. Data were analyzed using univariate analysis. Statistical differences were identified using student's t-test for normally distributed continuous data and the chi-squared test for categorical data. Nonnormally distributed variables were compared using the Mann–Whitney U test and reported as medians with interquartile ranges. Odds ratios and their 95% confidence interval (CI) were calculated for each risk factor. A p value less than 0.05 were considered statistically significant.

Results

Table 2 presents the sociodemographic characteristics of 271 participants, comprising 175 natural postmenopausal women and 96 surgical postmenopausal women. The overall mean age was 56.4 ± 8.2 years (ranging from 36 to 83 years), and the mean age at menopause was 49.8 ± 5.8 years. The majority (64.6%) of participants were postmenopausal, with an average age at menopause of 48.8 ± 4.9 years. Most participants were married, multiparous, and highly educated. The monthly household income ranged from 20,001 to 50,000 Baht, with over 40% of the participants employed by private or governmental organizations. Current hormone therapy usage was 24.5%, and surgical postmenopausal women had a significantly higher usage rate than natural postmenopausal women (42.7% vs 14.9%, $p < 0.001$). Among all participants, 65.3% had pre-existing medical conditions, with 21.8% having two or more diseases. The prevalence of pre-existing medical conditions was significantly higher among natural postmenopausal women than in surgical postmenopausal women (74.9% vs 47.9%, $p = 0.001$). The overall COVID-19 vaccination rate was 97.4%, and 26.9% of participants reported having been infected with COVID-19. Additionally, 38.4% of households had experienced a COVID-19 infection, but there were no significant differences in the rates for the natural and surgical postmenopausal groups.

Table 3 details the prevalence of depression as measured by the Thai Depression Inventory. The study found an overall prevalence of 9.6% among menopausal women during the COVID-19 pandemic, with surgical postmenopausal women having a higher rate (11.5%) than natural postmenopausal women (8.6%). However, there was no significant difference in the depression prevalence of the 2 subgroups. In contrast, the severity of depression in the surgical and natural menopausal groups differed significantly, with a higher prevalence of mild depression among surgical menopausal women (11.5%) than among natural menopausal women (4.0%, $p = 0.022$).

Table 2. Characteristics of 271 postmenopausal Thai women.

	All subjects (n = 271)	Menopausal status	
		Natural (n = 175)	Surgical (n = 96)
	mean ± SD or n (%)	mean ± SD or n (%)	mean ± SD or n (%)
Age, years (a)	56.4 ± 8.2	58.4 ± 7.4	52.7 ± 8.2
Age at menopause, years (a)	49.8 ± 5.8	48.8 ± 4.9	
BMI, kg/m^2	24.2 ± 4.5	24.3 ± 4.5	24 ± 4.6
Marital status, single	75 (27.7)	47 (26.9)	28 (29.2)
Nulliparity	101 (37.3)	58 (33.1)	43 (44.8)
Education			
None	2 (0.7)	2 (1.1)	0 (0)
Primary school	49 (18.1)	34 (19.4)	15 (15.6)
Secondary school	53 (19.6)	32 (18.3)	21 (21.9)
Associate's degree	27 (10.0)	19 (10.9)	8 (8.3)
Bachelor's degree and above	140 (51.7)	88 (50.3)	52 (54.2)
Occupation			
Unemployed	65 (24.0)	45 (25.7)	20 (20.8)
Farmers	2 (0.7)	1 (0.6)	1 (1.0)
Retired	44 (16.2)	35 (20.0)	9 (9.4)
Employee in an organization	122 (45.0)	74 (42.3)	48 (50.0)
Merchant	38 (14.0)	20 (11.4)	18 (18.8)
Household income, Baht/month			
≤ 20,000	90 (33.2)	60 (34.3)	30 (31.3)
20,001 - 50,000	111 (41.0)	66 (37.7)	45 (46.9)
> 50,000	70 (25.8)	49 (28.0)	21 (21.9)
Hormone therapy status (a)			
Never used	204 (75.3)	149 (85.1)	55 (57.3)
Current user	67 (24.7)	26 (14.9)	41 (42.7)
Duration of hormone therapy			
< 1 yr	20 (7.4)	8 (4.6)	12 (12.5)
≥ 1 yr	47 (17.3)	18 (10.3)	29 (30.2)
Medical diseases (b)			
No	94 (34.7)	44 (25.1)	50 (52.1)
Diabetes mellitus	7 (2.6)	4 (2.3)	3 (3.1)
Hypertension	24 (8.9)	19 (10.9)	5 (5.2)
Dyslipidemia	29 (10.7)	23 (13.1)	6 (6.3)
Chronic kidney disease	2 (0.7)	2 (1.1)	0 (0)
Others	56 (20.7)	40 (22.9)	16 (16.7)
At least 2 diseases	59 (21.8)	43 (24.6)	16 (16.7)
COVID-19 vaccination, yes	264 (97.4)	170 (97.1)	94 (97.9)
Previous COVID-19 infection, yes	73 (26.9)	50 (28.6)	23 (24)
Family history of COVID-19 infection, yes	104 (38.4)	74 (42.3)	30 (31.3)

Comparison among the 2 menopausal groups were performed using student's t-test for continuous data, and the chi-squared test for categorical data; variables with statistical significance are labeled as (a) $p < 0.001$ or (b) $p = 0.001$.

SD: standard deviation, BMI: body mass index, NA: not applicable, Others: cancer, neurological disorders, respiratory disorders, gastrointestinal disorders, musculoskeletal disorders.

Table 3. Prevalence of depression using Thai depression inventory for 271 postmenopausal Thai women.

	Overall (n = 271)	Menopausal status	
		Natural menopause (n = 175)	Surgical menopause (n = 96)
	n (%) or median	n (%) or median	n (%) or median
Prevalence of depression	26 (9.6)	15 (8.6)	11 (11.5)
Factors of Thai depression inventory			
1	2.0 (1.0–5.0)	2.0 (1.0–4.0)	2.0 (1.0–5.0)
2	3.0 (1.0–3.0)	3.0 (1.0–3.0)	2.0 (1.25–3.0)
3	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)
4	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.25–2.0)
5	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)
6	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Severity			
No	245 (90.4)	160 (91.4)	85 (88.5)
Mild depression(a)	18 (6.6)	7 (4.0)	11 (11.5)
Less than major depression	7 (2.6)	7 (4.0)	0 (0)
Major depression	1 (0.4)	1 (0.6)	0 (0)
Sever major depression	0 (0)	0 (0)	0 (0)

Data were analyzed using the chi-squared test for categorical data and the Mann–Whitney U test for nonnormally distributed data.
Data are n (%), median (interquartile range, IQR) otherwise indicated. Variables with statistical significance are labeled (a) p = 0.022.
Six factors from 20 items
Factor 1, anxiety syndrome (items 5, 7, 8, 10, 15 and 17); factor 2, depression factor (items 1, 2, 6 and 14); factor 3, hypochondriacal factor (items 16 and 18); factor 4, somatic symptoms of anxiety (items 9, 13 and 19); factor 5, somatic symptoms of depression (items 3, 11, 12 and 20); factor 6, psychomotor retardation (item 4).

Table 4 lists the KAPs related to COVID-19 and their associations with depression. Individuals with superior knowledge or attitudes toward COVID-19 had a lower prevalence of depression. Conversely, participants with high levels of preventive behavior had a higher prevalence of depression. However, these differences were not statistically significant.

Table 4. Knowledge, attitudes, and preventive practices of COVID -19 related to depression using the Thai Depression Inventory for 271 postmenopausal Thai women.

Factors	Non-depression n = 245, n (%)	Depression n = 26, n (%)	OR (95% CI)	p value
Knowledge				
Low	3 (1.2)	0 (0)	NA	
Middle	50 (20.4)	8 (30.8)	1.7 (0.7–4.2)	0.2
High	192 (78.4)	18 (69.2)		
Attitude			1.1 (0.5–2.5)	0.8
Low	116 (47.3)	13 (50)		
High	129 (52.7)	13 (50)		
Preventive behavior			0.9 (0.4–2.1)	0.9
Low	154 (62.9)	16 (61.5)		
High	91 (37.1)	10 (38.5)		

Data were analyzed using the chi-squared test for categorical data.
CI: confidence interval, NA: not applicable, OR: odds ratio.

Table 5 presents the factors associated with depression based on the Thai Depression Inventory. There was a significant difference in the prevalence of depression among menopausal women with monthly household incomes ≤ 20,000 Baht. However, there was no statistically significant difference in the prevalence of depression among women aged 50 and above, those who were married, or those with a body mass index < 23 kg/m².

Table 5. Factors associated with depression using the Thai Depression Inventory for 271 postmenopausal Thai women.

Factors	Non-depression n (%)	Depression n (%)	OR (95% CI)	p value
Age, yr			0.6 (0.2–1.5)	0.3
< 50 yr	44 (18.0)	7 (26.9)		
≥ 50 yr	201 (82.0)	19 (73.1)		
Marital status				
Single	65 (26.5)	10 (38.5)	2.1 (0.9–5.2)	0.1
Married	151 (61.6)	11 (42.3)		
Others	29 (11.8)	1 (3.8)	2.4 (0.8–7.3)	0.1
Household income, Baht/month				
≤ 20,000	75 (29.4)	15 (57.7)	3.3 (1.0–10.4)	0.04
20,001–50,000	104 (42.4)	7 (26.9)	1.1 (0.3–3.9)	0.9
> 50,000	66 (55.5)	4 (15.4)		
BMI, kg/m2			1.3 (0.6–2.9)	0.6
≤ 23 kg/m²	109 (44.5)	10 (38.5)		
> 23 kg/m²	136 (55.5)	16 (61.5)		
Medical diseases, CKD			20.3 (1.8–232.5)	0.02
No	244 (99.6)	24 (92.3)		
Yes	1 (0.4)	2 (7.7)		

Data were analyzed using chi-squared test for categorical data.
Others = divorce/separated/widowed.
BMI: body mass index, CI: confidence interval, CKD: chronic kidney disease, OR: odds ratio

Discussion

The first case of COVID-19 in Thailand was identified on January 13, 2020. By the end of 2021, the country had confirmed its first case of the Omicron variant. From early 2022, the rapidly increasing Omicron strain infections supplanted the Delta strain, leading to daily case numbers in the tens of thousands. As of September 2022, there were approximately 4.7 million cumulative cases and 30,000 deaths[18, 19]. Nevertheless, the severity of the disease also steadily decreased due to widespread vaccination and the attainment of sufficient immunity levels in the general population. The daily case numbers gradually fell to less than 100, indicating that the situation was being controlled. On October 1, 2022, the Thai government reclassified COVID-19 as a communicable disease under surveillance. Since then, the economy and society have been steadily recovering.

During the COVID-19 pandemic, the prevalence of depression among postmenopausal Thai women was 9.6%, as measured by the Thai Depression Inventory. This screening instrument, which measures the severity of depression, demonstrated satisfactory validity and reliability when evaluated with the Hamilton Rating Scale[20]. Six factors are assessed by the TDI: anxiety syndrome, depression factor,

hypochondriacal factor, somatic symptoms of anxiety, somatic symptoms of depression, and psychomotor retardation. The construction of each factor was founded not only on theoretical concepts of symptomatology, but also on the common manifestations of distress among Thai depressed subjects. This instrument was developed using data from the Thai population, so cultural differences are not a concern. Therefore, it is helpful to identify which component of the survey participants scored the highest to help distinguish postmenopausal symptoms and improve treatment outcomes.

The prevalence of depression observed in the current investigation (9.6%) was lower than the previously reported depression prevalence in the general Chinese population during the initial phase of the COVID-19 epidemic (16.5%). The differing results can be attributed to the timing of data collection. In the present study, data were collected 3 years after the pandemic outbreak, as opposed to early in the pandemic. By this later time point, individuals had adapted to a 'new normal' way of life, making adjustments in their careers, schools, and businesses. In other words, the situation was being managed, allowing individuals to resume a semblance of normalcy in their lives. Our research also indicated that participants with higher levels of knowledge or attitudes had a lower prevalence of depression, whereas those with high levels of preventative practices had a higher prevalence of depression. However, no statistically significant differences were found.

Compared to other studies, the prevalence of depression among postmenopausal Thai women during the COVID-19 pandemic was lower. Before the pandemic, Ahlawat et al[21] reported a prevalence of 38.3% among women with mild depression and 3.3% among women with moderate depression in Delhi. An et al[22] reported a prevalence of 2.8% in postmenopausal women in Korea prior to the pandemic. Differences in tools, cultural factors, and sociodemographic data may account for these varying results. There was no significant difference in the prevalence of depression among postmenopausal women between the pre-pandemic and the late-pandemic periods. Nonetheless, our findings contributed to a better understanding of the prevalence of depression in postmenopausal Thai women during the pandemic, which is crucial for implementing appropriate treatment and prevention measures.

During the initial phase of the COVID-19 outbreak in China[5], higher psychological impact was associated with female gender, lack of education, special physical symptoms, and a history of chronic illness. The present study found a higher prevalence of depression among low-income women. Additionally, women with chronic kidney disease were more likely to experience depression. However, adjusting for these factors through multiple logistic regression did not significantly alter these associations. Diabetes mellitus, hypertension, and dyslipidemia, as well as the presence of two or more underlying diseases, were not statistically associated with depression. This could be the participants whose conditions were stable. Similar to the study conducted in Delhi by Ahlawat et al[21], which suggested that depression was more common in postmenopausal women with lower socioeconomic status. Depression was more prevalent among those with chronic kidney disease (CKD) compared to the general population. In a prior study conducted in Taiwan, Chiang et al[23] reported a prevalence of depression of 22.6% among CKD patients who were not receiving dialysis treatment.

The prevalence of mild depression was 11.5% greater in women who underwent surgical menopause. A similar study conducted in Taiwan by Lin et al[24] also found that oophorectomy increased the overall risk of depression. However, Gibson et al[25] in the United States demonstrated that hysterectomy with or without ovarian conservation did not have a lasting negative effect on the mood of middle-aged women when compared to natural menopause. Although hormone therapy was found to be concurrently related to decreased anxiety and depression, there is uncertainty about its effect on depression symptoms in older women. It is possible that the decrease in depression

scores resulted from reduced vasomotor symptoms or estrogen's direct effects. Estrogen may function as an antidepressant by influencing neurotransmitter activity in the central nervous system, such as that of norepinephrine, serotonin, and dopamine. The differences in findings may be attributed to the use of hormone therapy and menopausal symptoms. Therefore, menopausal symptoms should be assessed in future research.

Our study has several limitations that must be taken into account. First, since the data were collected after the outbreak, participants may have responded differently to the questionnaire and interview items than they would have during the pandemic. Second, the COVID-19 situation was constantly evolving, and participants may have experienced varying degrees of stress. Third, the information surrounding the quarantine period for COVID-19 has changed, which may have affected the validity of the 12th knowledge question, which asks about the duration of quarantine. Nevertheless, this study adheres to the original information. Fourth, the study did not consider menopausal symptoms, such as vasomotor symptoms, pre-existing neurocognitive illnesses, such as dementia, which may be associated with an increased risk of depression. Fifth, the participants in our study were postmenopausal women who visited the Gynecologic Endocrinology Clinic at Siriraj Hospital, which may constrain the applicability of the results to rural populations and other healthcare systems. Last, an oversampling of a subgroup of peers (e.g., employed, retired) resulted in selection bias.

Conclusion

The prevalence of depression in postmenopausal Thai women during COVID-19 was 9.6%. Low household income and chronic kidney disease were significant predictors.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Risk Assessment of Endometrial Hyperplasia and Cancer in Premenopausal Women with Abnormal Uterine Bleeding

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ABSTRACT

Objectives: Our goal was to develop an endometrial sampling protocol for the early detection and treatment of endometrial hyperplasia and endometrial cancer (EH/EC) in premenopausal women experiencing abnormal uterine bleeding.

Materials and Methods: A prospective cohort study on premenopausal women with abnormal uterine bleeding who underwent endometrial sampling was conducted at Ratchaburi Hospital. Each patient's risk factors and conducted clinical assessments, including pelvic examinations and transvaginal ultrasound were documented. To determine the likelihood of EH/EC, univariate and stepwise logistic regression analyses were used.

Results: Among 200 eligible premenopausal women with abnormal uterine bleeding who received endometrial sampling, histological analysis identified EH in 14 women (7%) and EC in 7 women (3.5%). Stepwise logistic regression revealed a significant association of EH/EC with a body mass index of 30 kg/m^2 or higher, tamoxifen usage, and an endometrial thickness exceeding 10 mm ($p = 0.004$, 0.041, and 0.001, respectively). The presence of two or three of these risk factors significantly increased the association with EH/EC ($p < 0.001$).

Conclusion: Obesity, tamoxifen usage, and endometrial thickness greater than 10 mm were strong indicators of EH/EC. Endometrial sampling is recommended for patients exhibiting more than one of these risk factors.

Keywords: abnormal uterine bleeding, endometrial cancer, endometrial hyperplasia, endometrial sampling, model of endometrial sampling indication.

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การประเมินความเสี่ยงของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูก ในสตรีวัยก่อนหมดประจำเดือนที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูก

มรกต สุวรรณวนิช

บทคัดย่อ

วัตถุประสงค์*: เพื่อหาข้อบ่งชี้ที่เหมาะสมในการดูดเยื่อบุโพรงมดลูกส่งตรวจทางพยาธิวิทยาของผู้ป่วยที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูก ในกลุ่มวัยก่อนหมดประจำเดือน*

วัสดุและวิธีการ*: เป็นการศึกษาไปข้างหน้า ศึกษาผู้ป่วยที่มาด้วยอาการเลือดออกผิดปกติจากโพรงมดลูกในกลุ่มวัยก่อนหมดประจำเดือนที่ได้รับการดูดเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยาที่มารับบริการที่โรงพยาบาลศูนย์ราชบุรี โดยกลุ่มศึกษาทุกรายจะได้รับการบันทึกข้อมูลส่วนตัว ตรวจภายใน และตรวจ คลื่นเสียงความถี่สูงทางช่องคลอด เพื่อนำข้อมูลมาวิเคราะห์ความสัมพันธ์ของการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูกทางสถิติ*

ผลการศึกษา*: ผู้ป่วยที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูกที่ได้รับการดูดชิ้นเนื้อในโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยาจำนวน 200 ราย พบว่ามี 14 ราย (ร้อยละ 7) ที่พบภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และพบมะเร็งโพรงมดลูก 7ราย (ร้อยละ 3.5) จากการศึกษาทางสถิติพบว่าผู้ป่วยที่มีภาวะอ้วน ผู้ที่รับประทานยา tamoxifen ความหนาของโพรงมดลูกมากกว่า 10 มิลลิเมตร มีความสัมพันธ์ต่อการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูกทางสถิติ ($p = 0.004, 0.041, 0.001$ ตามลำดับ) อีกทั้งยังพบว่าหากมีความเสี่ยงมากกว่า 1 ใน 3 ข้อนี้จะยิ่งเพิ่มความเสี่ยงได้สูงมากขึ้นด้วย*

สรุป*: ผู้ป่วยที่มีเลือดออกผิดปกติจากโพรงมดลูกในวัยก่อนหมดประจำเดือน ที่มีความเสี่ยงมากกว่า 1 ใน 3 ข้อนี้ (ภาวะอ้วน ผู้ที่รับประทานยา tamoxifen หรือ ผู้ที่มีความหนาของโพรงมดลูกมากกว่า 10 มิลลิเมตร) ควรได้รับการดูดเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยา*

คำสำคัญ*: เยื่อบุโพรงมดลูกหนาตัวผิดปกติ มะเร็งโพรงมดลูก ดูดเยื่อบุโพรงมดลูก เลือดออกผิดปกติจากมดลูก*

Introduction

Abnormal uterine bleeding (AUB), characterized by symptoms such as heavy menstrual flow, bleeding between periods, menometrorrhagia, and irregular cycles, is a frequent issue, affecting an estimated 14.25% of women in their reproductive years[1]. Its causes range from nonspecific dysfunctional uterine bleeding to endometrial carcinoma. Comprehensive evaluation is crucial, especially in perimenopausal patients, where the risk of endometrial carcinoma ranges from 10% to 15%[2]. Notably, AUB is the initial symptom in approximately 75% - 90% of endometrial cancer (EC) cases[3]. In postmenopausal women with AUB, the risk of EC is approximately 10%[4], but this risk decreases to under 1% if transvaginal ultrasonography indicates an endometrial thickness (ET) of less than 4 mm.[5]

For premenopausal women with AUB, however, this risk assessment is less clear due to the inconsistent predictive value of ET[6-7]. In these cases, other clinical factors, such as obesity, never having been pregnant, infertility, metabolic syndrome, tamoxifen use, and anovulation, are considered in assessing the risk of endometrial hyperplasia and endometrial cancer (EH/EC)[8-10].

In the United States, endometrial evaluation typically involves transvaginal ultrasound and endometrial sampling, often accompanied by hysteroscopy. However, there is no agreed-upon protocol regarding the optimal sequence or combination of these procedures. Establishing absolute risk estimates is key for effective guidance[11-13].

The aim of this study was to develop a model for determining when endometrial sampling is indicated, facilitating early diagnosis and treatment of EH/EC in premenopausal women experiencing AUB.

Materials and Methods

This study was a prospective cohort analysis conducted at Ratchaburi Hospital. It involved premenopausal women with AUB who underwent endometrial sampling between November 2021 and October 2022. The study's protocol received approval from Ratchaburi's Human Research Ethics Committee. Prior to participation, eligible subjects received detailed information about the study and provided their written informed consent.

Sample size calculation

To determine the sample size, we reviewed the medical records of premenopausal AUB patients at Ratchaburi Hospital. The prevalence of EH/EC was found to be 0.3. Using the formula from Bartlett et al[14] in Fig. 1. we calculated that a minimum of 150 cases was necessary. The study included peri- or premenopausal women with AUB who consented to participate. We excluded women in menopause and those with early menarche (less than 2 years), previous pelvic radiation, endometrial sampling within the last 6 months, current pregnancy, postabortion within 3 months, or systemic diseases. Women with bleeding from cervical or vaginal lesions were also excluded.

$$n = \frac{z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{d^2}$$

Fig. 1. Sample size calculation.

n (sample size). P (expected prevalence or proportion). d (deviation errors = 0.05). z (statistic for a level of confidence)

Clinical evaluation

In this study, premenopausal women with AUB underwent the following clinical evaluations: (a) a pelvic examination to exclude vaginal and cervical lesions, (b) transvaginal ultrasound, conducted by a gynecological doctor, to measure ET. This was done by viewing the uterus's sagittal section to measure the endometrium line from one basalis layer to the other. The thickness was recorded in millimeters, and (c) endometrial sampling using either a Pipelle device or dilation and curettage. Samples were examined by gynecologic pathologists.

Statistical analysis

In the statistical analysis, continuous variables were presented as medians and interquartile ranges, while qualitative variables were shown as counts and percentages. Univariate logistic regression was used to analyze all independent variables, with results expressed as odds ratios (OR) and 95% confidence intervals (CIs). Multivariate logistic regression helped identify variables significantly associated with EH/EC. This analysis included variables that had a p value ≤ 0.25 in the univariate model. Categorical variable comparisons were made using the chi-square test, and relative risk was calculated to ascertain the association between one or more risk factors and EH/EC. All statistical analyses were conducted using IBM SPSS Statistics, version 23 (IBM Corp, Armonk, NY, USA), considering a p value < 0.05 as statistically significant.

Results

In this study, 200 eligible premenopausal patients with AUB underwent endometrial sampling at Ratchaburi Hospital. The majority of AUB cases occurred in women aged 41–50 years (58%). Common characteristics among these patients were obesity (27%), nulliparity (17.5%), hypertension (17%), dyslipidemia (12.5%), diabetes (9.5%), and tamoxifen use (9.5%). Transvaginal ultrasound revealed that 38% of the AUB patients had an ET thickness greater than 10 mm. Histological examination of endometrial samples identified 14 women (7%) with EH and 7 women (3.5%) with EC (Table 1).

Table 1. Baseline patient characteristics among women with abnormal uterine bleeding.

Characteristic	Study participants (n=200) Number (%)
Age(years)	
< 30	6 (3.0)
31 - 40	42 (21.0)
41 - 50	116 (58.0)
> 50	36 (18.0)
BMI ≥ 30 (kg/m^2)	54 (27.0)
Nulliparous	35 (17.5)
Type II diabetes	19 (9.5)
Hypertension	34 (17.0)
Dyslipidemia	25 (12.5)
Metabolic syndrome	6 (3.0)
Tamoxifen user	19 (9.5)
PCOS	8 (4.0)
Endometrial thickness > 10 mm.	76 (38.0)
Histology	
Endometrial cancer	7 (3.5)
Endometrial hyperplasia	14 (7.0)
Proliferative endometrium	90 (45.0)
Secretory endometrium	38 (19.0)
Endometrial polyp	51 (25.5)

BMI: body mass index, PCOS: polycystic ovarian syndrome

Univariate logistic regression analysis indicated significant associations of EH/EC with a body mass index ≥ 30 kg/m^2 (OR 20.46, 95% CI 3.04 - 137.58, p = 0.002), tamoxifen use (OR 13.04, 95% CI 1.25 - 135.88,p = 0.032), and an ET > 10 mm (OR 15.61, 95% CI 2.34 - 104.28, p = 0.005) (Table 2).

Table 2. Univariate logistic regression: factors associated with endometrial hyperplasia and endometrial cancer.

Variables	OR	95% CI	p value
BMI ≥ 30 kg/m^2	20.46	3.04 to 137.58	0.002
Nulliparous	3.50	0.49 to 24.99	0.211
Type II diabetes	0.39	0.02 to 7.36	0.533
Hypertension	1.31	0.23 to 7.58	0.760
Dyslipidemia	1.99	0.17 to 23.32	0.580
Tamoxifen user	13.04	1.25 to 135.88	0.032
PCOS	1.51	0.68 to 33.64	0.790
Endometrial thickness > 10 mm.	15.61	2.34 to 104.28	0.005

BMI: body mass index, CI: confidence intervals, EH/EC: endometrial hyperplasia/endometrial cancer, OR: odds ratio, PCOS: polycystic ovarian syndrome

Multivariate analysis using the stepwise method confirmed significant associations of EH/EC with a body mass index ≥ 30 kg/m^2 (95% CI 1.54 - 147.59, p = 0.004), tamoxifen use (95% CI 1.33 - 165.76, p = 0.041), and ET > 10 mm (95% CI 5.66 - 134.95, p = 0.001). Factors not included in the model were nulliparity, type II diabetes mellitus, hypertension, dyslipidemia, and polycystic ovary syndrome (Table 3).

Table 3. Multivariate logistic regression: predictors of endometrial hyperplasia and endometrial cancer.

Variable	95% CI		p value
	Lower	Upper	
BMI ≥ 30 kg/m^2	1.54	147.59	0.004
Tamoxifen user	1.33	165.76	0.041
Endometrial thickness > 10 mm	5.66	134.95	0.001

* Using the stepwise method, variables that not included in the model were nulliparity, type II diabetes mellitus, hypertension, dyslipidemia, and polycystic ovary syndrome.
BMI: body mass index; CI: confidence interval

The study found that having two or three risk factors was significantly more prevalent in women with EH/EC than in controls (47.62% vs 5.03% and 19.05% vs 0%, respectively, p < 0.001). There was no significant difference in EH/EC prevalence among AUB patients with only one risk factor (Table 4). The analysis did not isolate individual risk factors for EH/EC but demonstrated that patients with two or three of these risk factors were strongly associated with EH/EC.

Table 4. Comparative analysis of risk factors in women with and without endometrial hyperplasia and endometrial cancer.

Risk factors (BMI > 30 kg/m^2, tamoxifen user, endometrial thickness > 10 mm)	Women without EH/EC n (%) 179 (100)	Women with EH/EC n (%) 21 (100)
None	97 (54.19)	0 (0)
1 risk factor	73 (40.78)	7 (33.33)
2 risk factors	9 (5.03)	10 (47.62)
3 risk factors	0 (0)	4 (19.05)

BMI: body mass index, EH/EC: endometrial hyperplasia/endometrial cancer

Discussion

This study revealed that the incidence of EH/EC in premenopausal women with AUB was 10.5%, aligning closely with previous reports suggesting a prevalence of 10% to 15% in this demographic[2, 9]. Despite this, the low overall incidence of the disease suggests that frequent endometrial sampling might be excessively invasive for this group. While factors such as type II diabetes, metabolic syndrome, and nulliparity have been strongly linked to EH/EC in other studies[13,15], this correlation was not statistically significant in our research. However, consistent with prior findings[15,17-19], obesity showed a strong association with EH/EC.

For postmenopausal women experiencing initial episodes of bleeding, transvaginal ultrasound is typically the primary diagnostic test, with biopsy recommended for those showing an ET greater than 4 mm. However, in premenopausal women with AUB, such risk stratification is challenging due to inconsistent results in the predictive accuracy of ET[6-7, 12]. In our study, transvaginal ultrasound was used to measure ET, and we found that an ET greater than 10 mm was significantly associated with EH/EC. In contrast, no EH/EC cases were observed in women with an ET of 4 mm or less. This finding aligns with previous studies that included ET in their multivariate models and identified a strong correlation between an ET greater than 10 mm and EH/EC[17-19].

Current guidelines advise considering various clinical risk factors, such as age, obesity, and the use of unopposed estrogen, in the assessment of premenopausal women with AUB. However, these guidelines do not provide clear directives on how to incorporate these factors into the decision-making process for endometrial sampling[8-10, 13, 15-16].

One of the main strengths of this study is its design as a prospective cohort study, which allowed for comprehensive data collection on risk assessment, pelvic examination, and ultrasound evaluation in women with AUB who underwent endometrial sampling. Nevertheless, a notable limitation of this study was the low prevalence of EH/EC in the sample. Additionally, the study's findings were somewhat limited by the small number of participants who had type II diabetes and metabolic syndrome in the premenopausal AUB group.

Conclusion

This study identified that obesity, tamoxifen use, and an ET greater than 10 mm were significantly associated with EH/EC. Therefore, endometrial sampling is recommended for patients exhibiting more than one of these risk factors.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

The Influence of Types of Gestational Diabetes Mellitus, Self-management, Social Support, and Risk Perception on Health-related Quality of Life in Pregnant Women with Gestational Diabetes Mellitus

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ABSTRACT

Objectives: This study aimed to investigate the factors influencing the health-related quality of life (HRQoL) in pregnant women with gestational diabetes mellitus (GDM).

Materials and Methods: Participants were 140 pregnant women with GDM who were receiving antenatal care at King Chulalongkorn Memorial hospital, Bangkok. Data were collected to obtain information including the self-management questionnaire, the social support questionnaire, perceived risk of GDM questionnaire, and gestational diabetes mellitus questionnaire-36 (GDMQ-36). Data were analyzed by using descriptive statistics, Pearson's product-moment correlation, point biserial correlation, and multiple linear regression.

Results: The results showed that the participants had diagnosed with GDMA1 and GDMA2 equal to 45.7% and 54.3%, respectively. The HRQoL of the participants were 62.06 and influenced by self-management, social support, and risk perception. The HRQoL would be increased if pregnant women had self-management effectively ($\beta = 0.236$, 95% confidence interval (CI) 0.201 to 0.586, $p < 0.001$), received social support ($\beta = 0.222$, 95% CI 0.199 to 0.672, $p < 0.001$), and received information in a proper level ($\beta = -0.644$, 95% CI -0.982 to -0.689, $p < 0.001$).

Conclusion: Improving HRQoL of pregnant women with GDM, health care providers should encourage pregnant women to have effective self-management, receive social support, and perceive the risks of GDM at an appropriate level.

Keywords: gestational diabetes mellitus, self-management, social support, risk perception, health-related quality of life.

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อิทธิพลของชนิดของภาวะเบาหวานขณะตั้งครรภ์ การจัดการตนเอง การสนับสนุนทางสังคม และการรับรู้ภาวะเสี่ยงต่อคุณภาพชีวิตในมิติสุขภาพในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์

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บทคัดย่อ

วัตถุประสงค์*: การศึกษาในครั้งนี้มีวัตถุประสงค์เพื่อศึกษาปัจจัยที่มีอิทธิพลต่อคุณภาพชีวิตในมิติสุขภาพในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์*

วัสดุและวิธีการ*: ศึกษาในสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์ จำนวน 140 ราย ที่เข้ารับบริการฝากครรภ์ที่โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย กรุงเทพมหานคร แบบสอบถามที่ใช้ในการเก็บรวบรวมข้อมูล ได้แก่ แบบสอบถามการจัดการตนเอง แบบสอบถามการสนับสนุนทางสังคม แบบสอบถามการรับรู้ภาวะเสี่ยงของภาวะเบาหวานขณะตั้งครรภ์ และแบบสอบถาม GDMQ-36 วิเคราะห์ข้อมูลโดยใช้สถิติพรรณนา สหสัมพันธ์ของเพียร์สัน สหสัมพันธ์แบบพอยท์ไบซีเรียล และการวิเคราะห์การถดถอยพหุคูณ*

ผลการศึกษา*: จากผลการศึกษา พบว่า กลุ่มตัวอย่างได้รับการวินิจฉัยภาวะเบาหวานขณะตั้งครรภ์ชนิดที่ 1 และ 2 จำนวนร้อยละ 45.7 และ 54.3 ตามลำดับ กลุ่มตัวอย่างมีค่าเฉลี่ยคะแนนคุณภาพชีวิตในมิติสุขภาพ เท่ากับ 62.06 คะแนน โดยปัจจัยที่ส่งผลกระทบต่อคุณภาพชีวิตในมิติสุขภาพ ได้แก่ การจัดการตนเอง การสนับสนุนทางสังคม และการรับรู้ภาวะเสี่ยง โดยคุณภาพชีวิตในมิติสุขภาพจะเพิ่มขึ้นเมื่อกลุ่มตัวอย่างมีการจัดการตนเองอย่างมีประสิทธิภาพ (β = 0.236, 95% CI 0.201 to 0.586, $p < 0.001$) ได้รับการสนับสนุนทางสังคม (β = 0.222, 95% CI 0.199 to 0.672, $p < 0.001$) และมีการรับรู้ภาวะเสี่ยงในระดับที่เหมาะสม (β = -0.644, 95% CI -0.982 to -0.689, $p < 0.001$)*

สรุป*: การส่งเสริมคุณภาพชีวิตในมิติสุขภาพของสตรีที่มีภาวะเบาหวานขณะตั้งครรภ์ เจ้าหน้าที่ทีมสุขภาพควรสนับสนุนให้สตรีตั้งครรภ์ มีการจัดการตนเองอย่างมีประสิทธิภาพ ได้รับการสนับสนุนทางสังคม และมีการรับรู้ภาวะเสี่ยงของโรคในระดับที่เหมาะสม*

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Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy, characterized by abnormal carbohydrate intolerance that causes pregnant women to struggle with controlling their blood glucose levels within the normal range[1]. Over the past 30 years, the prevalence of GDM has been approximately 14.0%[2]. In Asia, the prevalence of GDM varies widely, ranging from 1.2% to 49.5%, depending on individual characteristics and contextual factors[3]. In 2019 and 2020, the incidence of GDM at King Chulalongkorn Memorial hospital was 12.04% and 11.18%, respectively[4,5]. During pregnancy, especially in the second and third trimesters, physiological changes in placental hormones can lead to insulin resistance, resulting in elevated blood glucose levels[6], which lead complications to both mother and fetus. However, behavioral modifications including dietary controlling, exercising, self-monitoring blood glucose, or receiving pharmacological treatment can significantly improve maternal and fetal outcomes by maintaining blood glucose levels within the normal range[7]. Consequently, healthcare providers play an important role in providing care and encouraging pregnant women to modify health behaviors to effectively manage GDM[8].

All physiological and psychological changes in pregnant women all affect their well-being and health-related quality of life (HRQoL), which person's perception about health status, illness, and treatment that affect their physical, psychological, social, and role(9). If pregnant women go through normal changes until giving birth and are able to cope with their changes effectively, these will result in good HRQoL[10,11]. Conversely, pregnant women diagnosed with GDM often encounter negative experiences due to the unexpected diagnosis and may face barriers when attempting to follow medical recommendations. Additionally, they need to adhere to strict dietary restrictions to control their blood glucose levels, which can lead to frustration and feelings of loss of control[12-14]. Moreover, for those with GDM type A2, insulin injections can cause mental stress, further impacting their HRQoL[15-17].

HRQoL is one of the health indicators that reflects one's perception about illness and treatment based on the pregnant woman's life, mental status, stress limits in daily activities, or treatment burden. Almost of studies focus on general or some aspect of quality of life, which is quite difficult to evaluate and adapt in medical care[8,15,18,19]. To facilitate well-being through optimally effectiveness medical care for pregnant women with GDM, this study uses a gestational diabetes mellitus questionnaire-36 (GDMQ-36) as diabetic arising in pregnancy-specific measure[20]. Therefore, the researcher was interested in investigating factors influencing the HRQoL in pregnant women with GDM, providing valuable insights for the development of care plans aimed at enhancing HRQoL for this population.

Materials and Methods

The research proposal was approved by the Institutional Review Board on Research Involving Human Subject of the Faculty of Nursing, Mahidol university and the Faculty of Medicine, Chulalongkorn University. After that, this predictive study was conducted at antenatal care clinic, King Chulalongkorn Memorial hospital. The participant were 140 pregnant women with GDM, and inclusion criteria as follow; (1) aged 18 years old or older; (2) diagnosed with GDM at least one month before recruited in the study; and (3) gestational age between 24 to 42 weeks. Pregnant women with obstetrical complications, medical complications, psychiatric problems, and fetal abnormalities were excluded from this study.

The sample size calculation was performed using the G*Power program, relying on the correlation coefficient obtained from Ansarzadeh et al[18]. These findings led to the determination of the sample size through the square multiple correlation (R2 = 0.085), resulting in an effect size of 0.094. The power of the test was set at 0.80, with a significant level of 0.05 and four predictor variables. The desired sample size was 132, with an additional 7% added to account for potential nonresponse[18], resulting in a final participant

count of 140.

The data collection instrument comprised five parts, including:

(1) The demographic characteristics questionnaire.

(2) The self-management questionnaire, which was constructed by Radarith et al[21], has a content validity index (CVI) value of 1.0 and a Cronbach's alpha coefficient of 0.78, consists of 20 items categorized into four domains: dietary control, physical activity, glucose management, and medication. For participants with GDM type A1, items 1 to 17 were answered, while those with GDM type A2 responded to all 20 items, with items 18 to 20 specifically addressing medication. The questionnaire is based on a five-point Likert scale ranging from 0 to 3. The possible score range was 0 to 51 for GDM type A1 and 0 to 60 for GDM type A2. Subsequently, scores were transformed to a 0-100 scale, with higher scores denoting better self-management compared to lower scores.

(3) The social support questionnaire, the Tachasaksri et al[22] was used. CVI and a Cronbach's alpha coefficient was equal to 1.0 and 0.96, respectively. This questionnaire comprises 15 items organized into four domains: emotion, assistance with tasks, information, and material aid. It used a four-point Likert scale ranging from 1 to 4 with score ranging from 15-60 with higher scores indicating a greater level of perceived social support.

(4) Perceived risk of GDM questionnaire was developed by Untharin et al[23] and consists of 10 items. CVI and a Cronbach's alpha coefficient was equal to 1.0 and 0.89, respectively. Participants rated their responses using a five-point Likert scale ranging from 1 to 5. The potential score range for this questionnaire is 10 to 50, where a higher score indicates a greater perception of the risk associated with GDM compared to a lower score.

(5) The quality-of-life questionnaire for women with GDM (GDMQ-36) was originally designed by Mokhlesi et al[20], which a CVI value of 0.99 and a Cronbach's alpha coefficient of 0.93, and back translation by the researcher. This questionnaire comprises 36 items categorized into five subscales (concerns about high-risk pregnancy, perceived constraints, disease complications, medication and treatment, and support). Participants responded to the questionnaire using a five-point Likert scale ranging from 1 to 5. For participants with GDM type A2, all 36 items were completed, resulting in a score range between 36 to 180. Conversely, for those with GDM type A1, all items were answered except for 26, 27, 29, and 30, which pertain to medication. Consequently, their possible score range was 32 to 160. Subsequently, all scores were converted to a scale of 0 to 100, with higher scores indicating a better HRQoL than lower scores.

All the questionnaires underwent a validation process, which included assessment by one obstetrician and two midwifery lecturers. The results of CVI for all questionnaires were equal to 1. Regarding reliability, the questionnaires were tested on a sample of 30 pregnant women with GDM. The result of Cronbach's alpha of the self-management questionnaire, the social support questionnaire, perceived risk of GDM questionnaire, and GDMQ-36 were equal to 0.74, 0.90, 0.96, and 0.92, respectively.

Descriptive statistics, including the mean, standard deviation, and percentages, were used to describe the characteristics of the data. Pearson's product-moment correlation was used to assess the correlation between self-management, social support, and risk perception with HRQoL, while the type of GDM was examined using point biserial correlation. For determine the influencing factors for HRQoL, multiple linear regression analysis was employed, with a significance level set at 0.05.

Results

The mean age of the participants was 33.59 years (standard deviation (SD) = 4.83), with 97.9% of them being married, and 55.7% having completed a bachelor's degree or higher. About one-third (39.3%) of the participants were employed by companies, while 27.9% worked freelance. The mean monthly income

for participants was 42,485.71 baht (SD = 19,884.37). Additionally, 62.3% had a family history of diabetes mellitus, and 29.7% had a family history of hypertension. In terms of pre-pregnancy body mass index (BMI), 40% were in the normal range, while 50% were overweight or obese, with a mean pre-pregnancy BMI of 25.62 kg/m2 (SD = 5.27). A majority of participants (60.7%) were multiparous. The mean gestational age at the baseline visit was 32.11 weeks (SD = 4.33). Among the participants, 45.7% were diagnosed with GDM type A1, and 54.3% with GDM type A2. Regarding blood glucose levels, fasting glucose averaged 85.69 (SD = 11.86), one-hour postprandial glucose was 128.11 (SD = 19.84), and two-hour postprandial glucose was 107.34 (SD = 13.79). Among those with multiparous (37.7%) had been diagnosed with GDM (Table 1).

Table 1. Demographic and characteristics of participants (n = 140).

Characteristics	mean ± SD	n (%)
Mean age ± SD (years)	33.59 ± 4.83	
Married status		137 (97.9%)
Education		
Middle school		17 (12.1%)
Senior high school/Vocational Certificate		39 (27.9%)
Associate degree/High Vocational Certificate		6 (4.3%)
Bachelor's Degree or higher		78 (55.7%)
Mean income ± SD	42,485.71 ± 19,884.37	
Family history		
Diabetes mellitus		86 (62.3%)
Hypertension		41 (29.7%)
Others		11 (8.0%)
Pre-pregnancy BMI (kg/m^2)	25.62 ± 5.27	
Underweight (< 18.5)		14 (10%)
Normal (18.5 – 24.9)		56 (40%)
Overweight/obese (≥ 25.0)		70 (50%)
Multigravida		85 (60.7%)
Past obstetrics		
GDM		29 (20.7%)
Mean gestation ± SD	32.11 ± 4.33	
Type of GDM		
GDM type A1		64 (45.7%)
GDM type A2		76 (54.3%)
Blood glucose level (mg/dL)		
Fasting < 95		109 (77.9%)
1 hour-PP < 140		115 (82.1%)
2 hour-PP < 120		119 (85.0%)

SD: standard deviation, BMI: body mass index, PP: post prandial

Table 2. The participant's self-management, social support, risk perception, and HRQoL score (n = 140).

Variables	mean ± SD	n (%)
Self-management	85.37 ± 7.61	
High level		139 (99.3%)
Moderate level		1 (0.7%)
Low level		0 (0.0%)
Social support	52.96 ± 6.49	
High level		115 (82.1%)
Moderate level		25 (17.9%)
Low level		0 (0.0%)
Risk perception	31.89 ± 9.81	
High level		40 (28.6%)
Moderate level		75 (53.6%)
Low level		25 (17.8%)
HRQoL	62.06 ± 12.72	
High level		24 (17.1%)
Moderate level		95 (67.9%)
Low level		21 (15.0%)

HRQoL: health-related quality of life, SD: standard deviation

The study findings revealed that participants reported a high level of self-management (mean = 85.37, SD = 7.61) and a high level of social support (mean = 52.96, SD = 6.49). They had a moderate level of risk perception (mean = 31.89, SD = 9.81) and a moderate level of HRQoL (mean = 62.06, SD = 12.72) (Table 2).

The correlation between variables is shown in Table 3. Statistically significant factors associated with HRQoL were type of GDM ($r = -0.250$, $p < 0.05$), self-management ($r = 0.358$, $p < 0.01$), social support ($r = 0.277$, $p < 0.01$) and risk perception ($r = -0.682$, $p < 0.01$). In terms of independent factors influencing HRQoL, multiple linear regression analysis was conducted (Table 4). The study revealed that the type of GDM, self-management, social support, and risk perception collectively predicted HRQoL among pregnant women with GDM, accounting for 59.4% of the variance ($R2 = 0.594$, $p < 0.001$). Notably, self-management ($\beta = 0.236$, 95% confidence interval (CI) 0.201 to 0.586, $p < 0.001$), social support ($\beta = 0.222$, 95% CI 0.199 to 0.672, $p < 0.001$), and risk perception ($\beta = -0.644$, 95% CI -0.982 to -0.689, $p < 0.001$) were significant predictors of HRQoL.

Table 3. Correlation of study variables (n = 140).

	1	2	3	4	5
1. type of GDM (r_{pb})	1				
2. self-management (r)	0.145	1			
3. social support (r)	-0.430**	0.190*	1		
4. risk perception (r)	0.214*	-0.134	0.009	1	
5. HRQoL (r)	-0.250*	0.358**	0.277**	-0.682**	1

*p < 0.05, **p < 0.01, rpb = Point biserial correlation, r = Pearson's product moment correlation, GDM: gestational diabetes mellitus (GDM), HRQoL: health-related quality of life, r_{pb} = Point biserial correlation, r = Pearson's product moment correlation

Table 4. Multiple linear regression for predicting HRQoL among participants (n = 140).

Variables	β	Std. Error	p - value	95% CI
constant		9.515	0.001	13.803, 51.438
Self-management	0.236	0.098	< 0.001	0.201, 0.586
Social support	0.222	0.120	< 0.001	0.199, 0.672
Risk perception	-0.644	0.074	< 0.001	-0.982, -0.689
$F = 49.470$, $p = .000$, $R^2 = 59.4\%$ (adjust $R^2 = 58.2\%$)				

Independent variables: type of gestational diabetes mellitus, self-management, social support, risk perception
HRQoL: health-related quality of life, Std. error: standard error, CI: confidence interval

The study findings revealed that participants reported a high level of self-management (mean = 85.37, SD = 7.61) and a high level of social support (mean = 52.96, SD = 6.49). They had a moderate level of risk perception (mean = 31.89, SD = 9.81) and a moderate level of HRQoL (mean = 62.06, SD = 12.72) (Table 2).

The correlation between variables is shown in Table 3. Statistically significant factors associated with HRQoL were type of GDM ($r = -0.250$, $p < 0.05$), self-management ($r = 0.358$, $p < 0.01$), social support ($r = 0.277$, $p < 0.01$) and risk perception ($r = -0.682$, $p < 0.01$). In terms of independent factors influencing HRQoL, multiple linear regression analysis was conducted (Table 4). The study revealed that the type of GDM, self-management, social support, and risk perception collectively predicted HRQoL among pregnant women with GDM, accounting for 59.4% of the variance ($R2 = 0.594$, $p < 0.001$). Notably, self-management ($\beta = 0.236$, 95% confidence interval (CI) 0.201 to 0.586, $p < 0.001$), social support ($\beta = 0.222$, 95% CI 0.199 to 0.672, $p < 0.001$), and risk perception ($\beta = -0.644$, 95% CI -0.982 to -0.689, $p < 0.001$) were significant predictors of HRQoL.

Discussion

From the beginning of diagnosis GDM, pregnant women received information about event that can occur during pregnancy and behavioral modifications, all of these involve with distress. So, pregnant women were likely to describe that GDM as stressful event. Regardless of GDM progression and treatment, some of pregnant women exhibited well-being. According to the study, the participants had a mean HRQoL score of 62.06 as a moderate level. This was analogous to prior research[16,17,19,24]; however, this study used GDMQ-36 as more disease-specific and valid for assessing quality of life in pregnant women with GDM. In accordance with the findings of this study, self-management– the ability to change behaviors in order to control blood glucose levels– affect the HRQoL in pregnant women with GDM which was complementary to previous research[15,18]. Good maternal and neonatal health outcomes through behavioral modifications including diet, exercise, and self-monitoring blood glucose level can be reduced stress[13]. This may be explained that receiving care from super tertiary care hospitals which offer specific and diverse self-care options, such as monitoring the mother's and fetus's health by an obstetrician, providing disease progression control by internists, providing diet care by nutritionists, and providing self-care training by nurses, results in effective blood glucose level management of pregnant women[7]. Stress and worry will be reduced if those pregnant women maintain routine bodily changes throughout their pregnancy without difficulties. HRQoL develops as a result. Thus, healthcare providers must assist pregnant women to self-manage in areas such as food, exercise, complications monitoring and assessment, and proper pharmacological treatment for successful and continuous treatment.

Similarly, the study discovered that social support could strongly predict HRQoL in women with

GDM. This was consistent with previous research that demonstrated peer support, particularly from husband, doctors, and nurses, greatly aid pregnant women with GDM[8]. It was noted that the majority of the participants were married, therefore they received pleasant comfort and understanding from their husbands. This is especially beneficial in dealing with illness and offering relaxation from strict behavioral changes. Furthermore, receiving efficient and continuous care from healthcare providers, receiving information on self-care and attending antenatal care with the same medical team throughout the pregnancy, or obtaining behavioral modification (e.g., blood glucose monitoring devices, mother class for GDM, telemedicine) will establish confident behavioral modification in pregnant women[14, 25], resulting in relaxation and less anxiety[26, 27]. To help pregnant women to manage gestational diabetes thoroughly, healthcare providers should provide both physical and psychological assistance, as well as promote participatory care from family or husband.

Furthermore, the study's findings demonstrated that risk perception can strongly predict HRQoL in women with GDM. When the participants maintained a high-risk perception, HRQoL declined. This might be analyzed to see if the participants were informed about the disease, as well as possible affections and consequences. Furthermore, they were subjected to more strict behavioral modifications than typical pregnant women. These may cause the perception that GDM is a serious illness, as well as anxiety and stress[12,28]. So that, HRQoL was declined. As a result, healthcare providers should deliver an appropriate level of information that promotes behavioral modifications without causing anxiety. Moreover, assessment for risk perception after receiving information about GDM should also be considered.

The following are some of the study's strengths. To begin, the study's design indicates the size of the influence of factors affecting HRQoL, providing an insightful awareness of the relevance of enhancing HRQoL in women with GDM. Second, unlike prior investigations, this study employed HRQoL questionnaires designed specifically for pregnant women with GDM rather than a general assessment. And this study demonstrated a high relationship between guidelines of care and HRQoL. Some limitations should be addressed, the sample size was small. Second, the context of the study setting differed in this study, making it inappropriate to generalize to primary and secondary care institutions. However, the findings of this study showed that the factors influencing HRQoL in pregnant women with GDM should encourage healthcare providers to collaborate in order to give better treatment guideline to pregnant women.

Conclusion

According to the findings of the study, self-management, social support, and risk perception can all affect the HRQoL in women with GDM. To improving HRQoL, emphasizing self-management to maintain normal blood glucose levels, promoting social support both physically and mentally, and providing acceptable and appropriate care based on the pregnant woman's life should be undertaken by healthcare providers simultaneously.

Potential conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Malignant Phyllodes Tumour in a Pregnant Woman Masquerading Clinically as an Abscess: A case report

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ABSTRACT

Phyllodes tumors (PT) are rare breast tumours comprising of < 1% of all breast tumours that arise from the stromal connective tissue of the breast. These tumors usually affect the adults of fifth and sixth decade and are rarely found in the pediatric or young age group. PT presents as a rapidly growing discrete palpable mass. Histologically, they are classified as benign, borderline, and malignant on the basis of histological features, mitotic index, necrosis, and infiltrative growth pattern. Malignant PT is a rare entity in pregnancy. We present a case of 27-year-old multigravida with one live male child and a term still born who presented to the outpatient department during antenatal visit with a rapidly growing breast lump early in the 25th week of gestation. Malignant PT becomes difficult to diagnose in a pregnant woman as lactation changes and clinical appearance can mask this diagnosis. A multidisciplinary approach is needed in such cases because there is a high recurrence rate and metastases when tumors are large, bulky with involved surgical margins.

Keywords: malignant, phyllodes, breast, pregnancy, abscess.

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Introduction

PT is a rare subset of fibroepithelial breast neoplasms with epithelial and stromal proliferation comprising 0.3 to 1% tumors that occur in female breast[1,2]. Characterized initially in 1838 by Johannes Muller as 'cystosarcomaphyllodes', the current endorsed designation is PT by the World Health Organisation (WHO)[3,4]. PT demonstrates heterogeneous behavior dictated by underlying pathological features and is classified into benign, borderline, and malignant categories. Benign PT simulates fibroadenoma and is prone to recurrence if not excised with wide margins, while malignant PT can exhibit distant metastasis via haematogenous route[3, 5, 6]. Usual presentation in PT is a breast lump. Higher incidence is reported in women of 4th to 5th decade, though they occur from puberty to menopause. Rapid enlargement mimics breast carcinoma, particularly if there is coexistent skin ulceration, nipple retraction, or fixation to the chest wall or overlying skin. Presentation during pregnancy is a rare event associated with marked increase in size.

Biopsy is the recommended tool for diagnosis, though occasionally immunohistochemistry may be required. Treatment of choice is wide surgical excision; however, revision surgeries may be required due to involved margins at initial excision[1,3].

Case Report

A 27-year-old female with G3P2, having a live male child aged seven and a term still born three years earlier, on a routine antenatal visit was referred to surgery OPD with a rapidly growing breast lump early in her 25th week of gestation. Four months ago, the patient had noticed a small lemon-sized lump in her left breast that had enlarged rapidly involving her entire breast causing immense discomfort. On examination a markedly enlarged left breast, firm to cystic on palpation, bearing shiny overlying skin and engorged superficial vessels measuring 22 X 18 centimetres was documented. No nipple retraction-inversion, skin ulceration, or fixation to the underlying tissues was evident. Axillary soft tissue was unremarkable on palpation. There was leucocytosis (13,880/mm^3) with neutrophilia (84%) and hypochromic microcytic anemia, probably due to multiple pregnancies and poor socioeconomic status of the patient leading to iron deficiency (haemoglobin: 8.6 g / dl, MCV: 62.5 fl, MCH: 21.7 pg) on hemogram. On ultrasonography a large loculated lesion with areas of organized component, low level echoes within lesion identified in left breast at 9 o'clock to 4 o'clock region. Radiologist suggested the possibility of galactocele or abscess (Fig. 1a). The surgeons performed incision and drainage (I&D), whereby 20-30 ml of serous fluid was drained and sent for pus culture. Although the patient had temporary relief following

I & D, the culture was sterile. Gram stain was not performed. Fine needle aspiration cytology (FNAC) showed cellular smears with sheets and clusters of atypical cells that were large in size, had high N: C ratio, hyperchromatic nuclei with prominent nucleoli, and vacuolated cytoplasm. These cells were admixed with stromal cells, hemosiderin macrophages, and red blood cells suggestive of malignancy (Fig. 1b & 1c). A core biopsy performed in the interim was suspicious of a phyllodes tumor, and a mastectomy with wide surgical margins was promptly performed.

The gross specimen received in surgical pathology was 19 x 16 x 6 centimetres. Serial sectioning identified solid cystic areas, the latter were filled with mucoid reddish fluid. The solid areas bore a tan appearance (Figs. 1d & 1e).

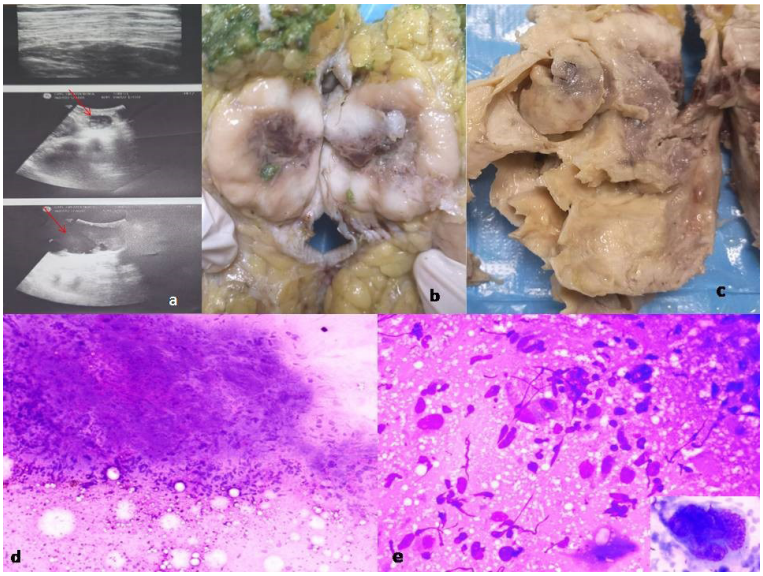

Fig. 1.

1a: Ultrasonographic imaging showing a large loculated lesion measuring approximately 23 x 19 cm in size with areas of organised component (low level echoes) (⇧)

1b: Cut surface of gross specimen of left breast showing grey white, firm solid, hemorrhagic area.

1c: Gross specimen of left breast showing grey white to tan, solid and cystic areas. The latter filled with mucoid reddish fluid

1d: Fine needle aspiration cytology (FNAC) of the lesion showing hypercellular smears displaying abundant stromal cells mixed with pleomorphic tumour cells (MGG; 40x).

1e: Fine needle aspiration cytology (FNAC) of the lesion showing scattered pleomorhic, hyperchromatic cells with scant amount of cytoplasm admixed with stromal cells in haemorrhagic and necrotic background. Inset showing a large, markedly plemorphic cells with prominent nucleoli. (MGG; 400x).

Representative sections examined demonstrated a markedly cellular tumor showing stromal overgrowth, nuclear and cellular pleomorphism, high mitotic index (33/10 high-power fields or 22/millimetre^2), bizarre giant cells, and focally present epithelial elements. Osseous metaplasia and myxoidsarcomatous changes were identifiable along with areas of necrosis (Figs. 2a, 2b, 2c, 2d). A diagnosis of malignant PT was rendered. Three of the four resected margins were involved. Tumor reached upto but did not affect the posterior resected surface. No lymph nodes were identified. The tissue resected bore fibroadenomatous foci in areas farther away from foci of phyllodes. The surgeons decided to wait for the patient to deliver the growing fetus at term before pursuing further surgery. The patient had confirmed a family history of breast cancer in her paternal grandmother who died one year after diagnosis and subsequent breast surgery, but due to lack of knowledge was not able

to share further details. Following sepsis due to severe urinary tract infection, the patient was induced and delivered a healthy male at 8 months of gestation. Breast surgery was re-performed three months after delivery with wide local excision repaired through latissimus dorsi flap. The posterior margins were affected in the frozen section, confirmed in histopathology. The patient received three cycles of Adriamycin-I-phosphamide post-surgery. Subsequently, she was referred to radiation oncologist. However, after 25 cycles of radio therapy, she returned to OPD with recurrence at the surgical margin. In the follow-up, the patient was not taking any treatment at the time of writing the article.

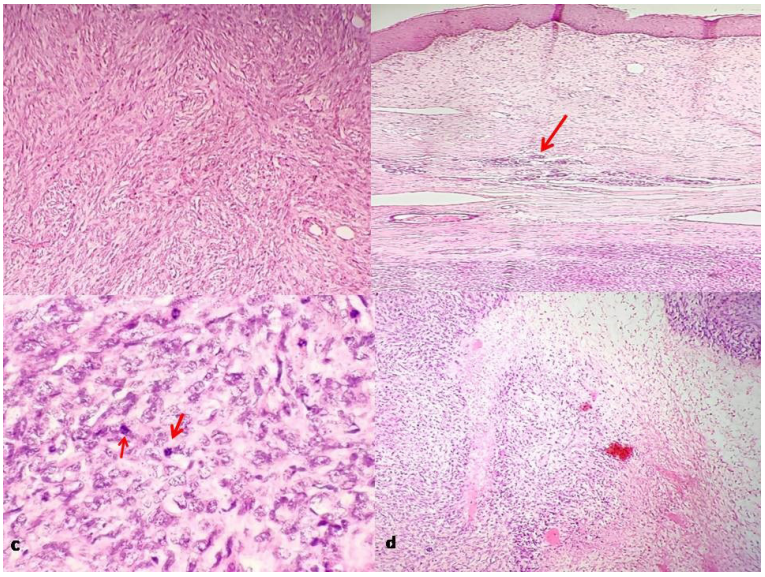

Fig. 2.

2a: Low power view of markedly cellular tumour showing stromal overgrowth arranged in fascicles and haphazardly with dilated and congested thick blood vessel (H&E; 100x).

2b: Normal breast acini (⇧) seen below the skin, beneath it highly cellular tumour seen with infiltrating pattern (H&E; 40x)

2c: spindled tumour cells displaying pleomorphism, hyperchromasia and vesicular chromatin with atypical mitosis (⇧) (H&E; 400x)

2d: Tumour cells with myxoid areas and necrosis (H&E; 100x).

Discussion

From its initial description by Johannes Muller in 1838 as "Cystosarcoma Phyllodes" derived from the Greek word phyllon to signify the macroscopic leaflike appearance, this entity has been subjected to various nomenclatures, the currently accepted term by WHO being PT[7]. Constituting < 1% of all breast tumors, PT are categorised into benign, borderline and malignant[8]. PT can be detected accidentally on ultrasound (US) examination or present as painless breast lumps of variable size (median range of 4-5 centimeters)[3]. According to the literature, PT occurs in older females (40-50 years of age) and malignant PT occurs even 2-5 years later than benign PT, the index case reported here is of a young female with malignant phyllodes[7]. Malignant PT is associated with rapid growth in pregnancy and can attain huge dimensions as highlighted in prior case reports[9].

Malignant PT accounts for approximately 6.5-27% of all PT[10]. Tumours of large sizes exhibit cystic changes and frequently areas of necrosis and hemorrhage, in the present case, cystic areas filled with mucoid material and hemoorhage were evident. However, areas of necrosis were not evident grossly[11]. Secondary changes like nipple retraction, discharge or tumour involvement of chest wall may occur simulating other breast carcinomas[3, 12]. Axillary lymph nodes are seldom involved and when palpable are in lieu of reactive causes[12]. Malignant PT are exceedingly rare and there occurrence in the breasts of pregnant women is even a rarer event. They may erroneously be misdiagnosed as benign and at times a delayed diagnosis due to apprehension regarding fetal outcomes can adversely affect management as in the present case report.

The literature has documented the rapid growth of all types of PT in pregnancy supporting the notion that they are hormone dependent[2,9]. Rapid growth of breast lump was recognized in present case yet erroneously misdiagnosed due to radiological, clinical and laboratory parameters unlike any of the previously cited case reports. This delayed the time excision of the mass. However, once excised and evaluated, the histopathology diagnosis was straightforward.

Histopathology is gold standard for diagnosis requiring diffuse and excessive stromal overgrowth along with marked nuclear pleomorphism and absence of epithelial elements in one low power microscopic field visualised by a 10x eyepiece 40 x magnifications and 4x objective[7]. Mitosis should be in excess of ≥ 10/10HPF of 0.5mm diameter, ≥ 5mitosis/mm^2 [7, 13].

The common differential diagnosis of phyllodes tumors includes fibroadenoma (intracanalicular pattern), sarcomas, periductal stromal tumor (PST), and metaplastic carcinoma. Both the fibroadenomas and phyllodes tumor show epithelial and connective tissue stromal elements, but higher stromal cellularity in PT helps to distinguish these two[14,15]. Primary breast sarcomas show high heterogeneity. Malignant PT is commonly misdiagnosed as pure breast sarcomas and vice a verse[14,16]. Desmoids fibromatosis, Angiosarcoma, inflammatory myofibroblastic tumor, leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma are the most common mesenchymal tumors of breast. Distinguishing them from each other may require collaboration of clinical features with histopathology and panel of immunohistochemistry (IHC) in some cases[7]. PT and PST share overlapping histological features, and the difference lies in the absence of leaflike fronds in PST. PST is characterized by proliferating spindle cells around open tubules and also, it is not circumscribed. Metaplastic carcinoma is another important differential diagnosis of malignant PT, but spindle cells in metaplastic carcinomas are positive for high molecular weight /basal cytokeratin such as 34 βE12 and CK 5/6 helps in resolving the problem[14, 17]. Diagnosis of PT can sometimes be arduous as overlap exists between benign PT and fibroadeoma and malignant PT with spindle cell sarcomas and metaplastic carcinomas. Intermediate PT can be confounding by itself due to lack of stringent diagnostic criteria and interobserver variation. When in doubt IHC can be resorted to. Cytokeratins CK 5/6, CKAE1/AE3, Cam 5.2 and 34 βE12 and p53 show variable positivity with sarcomatoid carcinoma while malignant PT is negative[18]. Markers for prediction of the outcome namely p53, EGFR, Ki 67 and PDGF are not particularly useful[2, 13].

Complete surgical excision is the standard treatment of choice (excision margins >1cm)[13]. Cases of malignant and borderline PT may additionally require adjuvant options like radiation and chemotherapy[2, 13]. The risk of recurrence and metastasis in tumors with involved resected margins is a potential possibility and hence a constant challenge to the surgeon. A lack of uniform guidelines in the management of pregnant malignant PT patients is an existing lacunae given the rare nature of the disease and should be addressed. However, rapid enlargement in size of PT has been documented in pregnancy. The present case has been reported to highlight its presentation as an mistaken diagnosis of an abscess both radiologically and clinically, leading

to the delayed treatment.

Conclusion

A high index of suspicion in pregnant women with rapidly enlarging breast masses will help in the timely diagnosis and management of malignant PT, as wide uninvolved resected margins are the end point that significantly improves prognosis for the patient. Delayed diagnosis, involved resected margins will subsequently require adjuvant techniques that may have financial and emotional consequences for the patient in the addition to worsening outcome as in present case.

Potential conflicts of interest

The authors declare no conflicts of interest.

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