ISSN 0857-6084

THAI JOURNAL OF OBSTETRICS AND GYNAECOLOGY

THE OFFICIAL JOURNAL OF
THE ROYAL THAI COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

VOL. 33 NO. 1 January - February 2025

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Thai Journal of Obstetrics and Gynaecology

Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

ISSN 0857-6084 E-ISSN 2673-0871

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Website: www.tci-thaijo.org, E-mail: vorapong.p@chula.ac.th

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Thai Journal of Obstetrics and Gynaecology

ISSN : 0857-6084. The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

Reviewer acknowledgement 2025

The editors would like to publicly acknowledge the people listed below who served as reviewers on the journal during 2024. Without their efforts, the quality of the journal could not be sustained. We appreciate their time and effort in evaluating papers and express our sincere thanks for their hard work and support.

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Thai Journal of Obstetrics and Gynaecology

The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

ISSN 0857-6084 E-ISSN 2673-0871

Vol. 33 No. 1 (JANUARY - FEBRUARY 2025)

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EDITORIAL

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

Vorapong Phupong, M.D., FRTCOG.*

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

This first issue of Thai Journal of Obstetrics and Gynaecology 2025 contains many interesting articles. The special article is "Molecular testing in endometrial cancer: An introduction from basic to practical point". The authors reviewed molecular issues in endometrial cancer. The contents included clarifying the terminology for molecular issues in endometrial cancer, the cancer genome atlas classification of endometrial cancers, proactive molecular risk classifier for endometrial cancer, and some practical point of molecular testing for endometrial cancer[1].

This issue also contains six original articles and two case reports. Thongaram et al performed a cross-sectional study to compare teenagers with unintended pregnancy that terminated their pregnancy and those who delivered using the Thai Edinburgh Postnatal Depression Scale (EPDS) and determine predisposing factors for depression. They found that there was no statistically significant difference in the total EPDS score between the two groups. No family support, dropout from school, and living alone were predisposing factors for depression[2]. Nathirojanakun performed a prospective randomized controlled trial to study the effect of Hemming stitch closure of the peritoneum at cesarean section on intra-abdominal adhesions and compare postoperative adhesion formation rate between the Hemming stitch closure group, the simple closure group, and the non-closure group. The result showed that Hemming stitch closure of the peritoneum at cesarean section reduces both the overall adhesion formation rate and the rate of severe adhesion[3]. Chupool et al performed a retrospective cohort study to compare the rate of large for gestational age (LGA) newborns between pregnant women with excessive weight gain (EWG) and appropriate weight gain. They found that EWG was associated with a higher rate of LGA in newborns and was likely to occur in women with higher pre-pregnancy body mass index and nulliparity[4]. Lertvanavit performed a cross-sectional study to evaluate the spike antibody level in the neonatal umbilical cord blood and serum of mothers vaccinated against coronavirus disease 2019 (COVID-19) during pregnancy and the association between the duration from the last vaccine dose to delivery and the spike Ab level. The result revealed COVID-19 vaccination during pregnancy can transfer antibody to newborn. The shorter duration of last dose of vaccination to delivery, the higher cord blood antibody[5]. Pongsupanimit et al performed a randomized controlled trial to investigate the impact of ginger supplementation on postoperative ileus following hysterectomy under the enhanced recovery after surgery protocol. They found that ginger supplementation did not significantly reduce the incidence of postoperative ileus or the recovery of bowel function following hysterectomy under the enhanced recovery after surgery protocol[6]. Chaiyakiat et al performed an online and paper-based questionnaires to determine the level of acceptance of COVID-19 vaccine among pregnant women residing in Thailand during

the COVID-19 pandemic and assess sociodemographic, medical and informational factors influencing their acceptance. The result showed fifty-nine percent of participants were willing to receive the Thai FDA-approved COVID-19 vaccines. Safety was the major reason for vaccine hesitancy[7].

Regarding case reports, Basri et al reported a rare case of idiopathic gestational gigantomastia presented at 15 weeks of gestation with painful bilateral breast swelling[8]. Puttanavijarn et al reported an uncommon case of intratumor hemorrhage in pedunculated subserosal leiomyoma mimic intraabdominal bleeding[9].

For the coming new year 2025, we would like to extend our warmest wishes to all members of Royal Colleague of Obstetricians and Gynaecologists, editorial board, reviewers, authors and families. We thank to all the authors, readers, reviewers, and editors for your great contributions to TJOG this past year and look forward to receiving your invaluable contributions in new year 2025.

Happy New Year 2025

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 3-12.

SPECIAL ARTICLE

Molecular Testing in Endometrial Cancer: An introduction from basic to practical point

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ABSTRACT

Endometrial cancer exhibits significant molecular heterogeneity, requiring precise classification for optimal management. The current landscape of molecular testing is examined, focusing on the comprehensive The Cancer Genome Atlas (TCGA) classification. This system stratifies endometrial cancers into four subtypes: POLE DNA polymerase epsilon (POLE) ultra-mutated, mismatch repair deficient (dMMR), p53-abnormal, and no specific molecular profile (NSMP). Each subtype's molecular characteristics, clinical features, and prognostic implications are detailed, including the roles of tumor mutational burden, copy number variation, and key genes such as tumor protein p53 (TP53). Molecular testing algorithms were explored. The clinical implications of each molecular subtype are discussed and emphasized their influence on prognosis and treatment. Simplified, some practical points were linked. Integrating molecular findings with clinicopathological data is highlighted as crucial for personalized patient management.

Keywords: endometrial cancer, mismatch repair, no specific molecular profile, p53, POLE ultramutation, The Cancer Genome Atlas classification.

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Received: 4 December 2024, **Revised:** 16 December 2024, **Accepted:** 27 December 2024

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries and the second most common in developing countries. In 2020, endometrial cancer was the fourth most common global female cancer[1]. There were 417,367 new diagnoses and 97,370 new deaths[2]. The incidence of this disease has been rising worldwide in recent decades. In Thailand, endometrial cancer was ranked the seventh most common female cancer, with age-specific incidence rates of 6.7 per 100,000 women-year, or there were 3,368 newly diagnosed in 2017[3]. The incidence of endometrial cancer increases annually; there were 1,573, 1,904, and 2,194 newly diagnosed

cases in 2008, 2011, and 2014, respectively[4-6]. This phenomenon is correlated with the incidence of overweight and obesity in Thai population[7]. Contributing factors to the rising incidence of this disease include increasing rates of obesity, sedentary lifestyles, and hormonal influences[8, 9]. Following significant changes in the staging of endometrial cancer as outlined by FIGO in 2023, an understanding of molecular testing has become critically important for staging the disease, prognosis, and treatment selection.

Bokhman's dualistic model is a foundational concept in understanding endometrial cancer, introduced by Dr. Alexander Bokhman in 1983. This model classifies endometrial cancers into two distinct types based on their clinical biological characteristics: tumor grade and histology type[10].

For Type I endometrial cancer, this estrogen-dependent disease is characterized by typically low-grade endometrioid tumors. It is associated with hormone exposure, particularly estrogen, and often develops in individuals with conditions such as obesity, Lynch syndrome, and polycystic ovarian syndrome[11]. Genetically, Type I tumors frequently exhibit mutations in the phosphatase and tensin homolog (PTEN), Kristen Rat Sarcoma Viral oncogene homolog (K-RAS), Catenin Beta 1 (CTNNB1), and phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) genes[12, 13]. Generally, Type I endometrial cancers have a better prognosis compared to Type II[14, 15].

Type 2 endometrial cancer typically arises in the context of an atrophic endometrium and includes high-grade tumors such as serous, clear cell, and undifferentiated carcinomas. Type II cancers are frequently associated with mutations in the TP53 gene as well as human epidermal growth factor receptor 2 (HER2) and v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2) genes[16]. These tumors tend to be more aggressive and are associated with a poorer prognosis[15].

Although Bokhman's dualistic classification provides insight into the clinical behavior and characteristics of endometrial tumors, it is nevertheless an oversimplification. This model fails to account for the complex interplay of molecular types and other nuances present in the molecular subtypes of endometrial cancer. Consequently, The Cancer Genome Atlas (TCGA) molecular classification was proposed in 2013, stratifying endometrial cancer into 4 molecular subtypes: POLE ultra-mutated, mismatch repair deficient (dMMR), p53 abnormality (p53abn), and no specific molecular profile (NSMP)[17]. Each subtype presents distinct recommendations for molecular testing algorithms, and there are even modified versions for scenarios where comprehensive testing is not feasible.

The mainstay of treatment for endometrial cancer is surgery, which involves the removal of the uterus and both adnexa. In low-risk cases, defined as endometrioid tumors of grade 1 or 2, with a tumor size less than 2 cm, myometrial invasion of less than 50%, pelvic lymphadenectomy may be omitted[18]. Additionally, sentinel lymph node lymphadenectomy can be considered for uterine-confined disease, even in patients with high-risk histology, as it may reduce complications associated with systematic lymphadenectomy[19, 20].

A thorough understanding of molecular classification and molecular testing is essential for optimizing prognosis and treatment strategies for patients with endometrial cancer. To the era of precision medicine, a personalized treatment, especially post operative adjuvant therapy, would be incorporated with the information from molecular testing, also the up-to-date standard guidelines.

Clarifying the terminology for molecular issues in endometrial cancer

1. Tumor mutational burden and copy number variation

Tumor mutational burden (TMB) is defined as the number of somatic coding mutations per megabase in a tumor. The TMB affects the major histocompatibility complex on the surface of tumor cells, facilitating the aggregation of tumor-specific T cells[21]. Tumor mutational burden-high (TMB-H) was defined as ≥10 mutations per megabase (mut/Mb). This aggregation leads to the formation of tumor-infiltrating lymphocytes[22],

which increases the likelihood of a response to immune checkpoint inhibitors as their mechanism acts on T cell receptor signaling transduction[23]. In terms of TGCA classification, POLE-ultramutated and dMMR are TMB-H, resulting in the tendency to respond to immune checkpoint inhibitors[23, 24].

Copy number variation (CNV), defined as a difference in the number of copies of a specific segment of DNA, can be caused by genomic, chemical, or physical factors[24]. Each histological type of endometrial cancer exhibits varying copy numbers at different chromosomal loci, influenced by distinct genes. Previous studies have attempted to correlate CNV with histological and molecular classifications that are associated with tumor prognosis. It was found that high CNV is prevalent in high-grade histology or in the p53-abnormal group based on molecular classification, whereas low CNV are observed in the NSMP group, which has a better prognosis[25].

2. Mismatch repair mechanism and microsatellite instability

Mismatch repair (MMR) proteins play an essential role in the repair of DNA errors. Among the MMR proteins, 4 have significant clinical relevance in human cancer: MLH1, MSH2, MSH6, and PMS2[26]. During DNA replication, mismatches can occur in the DNA sequence[27]. The repair process initiates with the recognition of a mismatch by the MSH proteins, which then recruit the MLH proteins to bind to the mismatch recognition signal[28]. After identifying the mismatch, the erroneous nucleotide-containing DNA strand is excised, and the final step involves DNA polymerase replicating the excised gap, followed by a ligation mechanism to restore the integrity of the DNA[28, 29].

In summary, MMR is a cellular mechanism that corrects spontaneous base-base mispairs and small insertion-deletion loops that occur during DNA replication, thus maintaining genomic stability[25]. Defects in this system can arise from somatic mutations, germline mutations, or epigenetic processes. Such defects lead to variations in the length of repeated sequences of DNA known as microsatellites. Changes in the length of microsatellites are indicative of microsatellite instability (MSI); thus, MSI is a consequence of defects in the MMR system.

3. Tumor protein P53 gene and p53 protein

The tumor protein p53 (TP53) gene, located on chromosome 17, provides instructions for the synthesis of a protein known as tumor protein p53 or p53[30]. It plays an important role in regulating the cell cycle, apoptosis, DNA repair, and cell senescence. The loss of TP53 function due to mutations promotes tumor proliferation and invasion because of the subsequent loss of its anti-tumor transcriptional activity[31]. Thus, this protein functions as a tumor suppressor. Somatic mutations of TP53 have been found in cancer tissues, while germline mutations in TP53 are associated with Li-Fraumeni syndrome[32], which predispose individuals to an increased risk of many types of cancer[33]. Missense mutation of TP53 leads to accumulation of p53 protein, which disrupts the nuclear localization signal in the cytoplasm of tumor cells[34].

4. DNA polymerase Epsilon (POLE)

Prior to cell division, the precise replication of DNA is essential for the prevention of mutations and tumorigenesis. Eukaryotic DNA replication attains a high degree of accuracy through the meticulous incorporation of nucleotides by DNA polymerases[35-37]. This process is further augmented by a proofreading mechanism that possesses DNA polymerase activity alongside 3'-5' exonuclease proofreading activity[38], which effectively removes mismatched nucleotides through the exonucleolytic action of DNA polymerase epsilon (POLE)[38, 39]. POLE mutations lead to somatic mutations associated with a high TMB. This induces cytotoxic T-cell activation and results in the dense formation of tumor-infiltrating lymphocytes and a favorable response to immune therapy[40].

TCGA classification of endometrial cancers

The TCGA has conducted an extensive analysis of the genomic and transcriptomic features of endometrial cancers through whole-exome massively parallel sequencing, as well as assessments of CNV and MSI. These endometrial cancers have been

classified into 4 genomic subtypes based on somatic mutational burden, somatic copy number alterations, and various molecular and histological markers in tumors. TCGA stratified endometrial cancer into 4 groups:

1. Ultra-mutated endometrial cancer (>100 mut/Mb): This group is characterized by pathogenic variations in the exonuclease domain of DNA polymerase epsilon (POLE).

2. Hypermutated endometrial cancer (10-100 mut/Mb): These tumors are microsatellite unstable due to dysfunctional mismatch repair proteins (dMMR).

3. Genomic stable, MMR-proficient endometrial cancer or copy number low: This group has a moderate number of mutations, mostly in phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt) and Wingless and Int-1 (Wnt) signaling pathways.

4. High somatic copy number alteration: Tumors in this category frequently exhibit pathogenic variants in TP53 (p53 abnormal, p53-abn).

Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)

The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular classifier stratified endometrial cancer into 4 prognostic groups mirroring TCGA outcomes based on the confirmed and validated molecular algorithm. The algorithm initially evaluates mismatch repair status through immunohistochemistry (IHC) for the MSH6 and PMS2 proteins. Next, POLE is tested by sequencing exons 9 to 14, followed by IHC analysis for p53.

1. POLE ultra-mutated endometrial cancer

Tumors with a polymerase ε exonuclease domain mutation (POLE-EDM) are associated with younger patients, lower body mass index (BMI). They typically present at an early stage, with 93.1% classified as stage I. Additionally, they predominantly exhibit endometrioid histology, accounting for 80% of cases. Patients with POLE-EDM tumors, which have been reported to account for 5-10% of endometrial cancer cases[37], demonstrate a favorable prognosis[40] according to the TCGA classification[42-47]. While POLE mutations are typically associated with low-grade endometrioid histology, nearly half of the POLE mutants exhibit high-grade histology, which includes endometrioid grade 3, as well as more aggressive histological types such as serous, clear cell, and carcinosarcoma[48, 49]. The prevalence of high-grade histology in POLE ultra-mutated endometrial cancer remains inadequately explained, but it may be attributed to a high mutational burden leading to substantial lymphocytic infiltration and alterations in chromatin structure[50].

It is important to emphasize that POLE mutation is one of the strongest prognostic markers for endometrial cancer[51]. A high TMB can indicate the presence of high-grade histological features or p53 mutations. Consequently, data supports the classification of POLE mutation alongside p53 abnormalities in endometrial cancer as representative of POLE mutation[51-53].

Clinical implication

Notably, regardless of p53 mutations or histological subtype, the POLE mutated group is least affected by histopathological factors[48]. Interestingly, some patients with POLE mutations may be at risk of overtreatment[46, 54]. For this reason, the European Society for Medical Oncology (ESMO) guideline in 2022 recommends the omission of adjuvant treatment for stage I/II POLEmut cancer and even for stage III POLEmut cancer. However, the evidence for omitting adjuvant treatment in stage III/IV POLEmut cancer is insufficient[55, 56].

2. MMR deficiency endometrial cancer

Estimate 30% of endometrial cancers have deficient MMR, which is mostly sporadic from hypermethylation. And only 3% of deficient MMR patients have germline mutation that are associated with Lynch syndrome[57]. MMR deficiency can be diagnosed through IHC, where the absence of one or more MMR proteins serves as a key indicator of such deficiency. Additionally, MSI can be assessed by analyzing the repeat lengths of specific microsatellite

markers, employing next-generation sequencing technologies. Previous studies have demonstrated a high degree of concordance between MMR testing via IHC and MSI testing using PCR techniques[58, 59].

Clinical implication

The MMR status of a tumor is a significant prognostic factor in endometrial cancer. Although it may not be as robust as the POLE mutation in predicting outcomes, existing literature indicates that tumors with deficient MMR (dMMR) are generally associated with a poorer prognosis compared to proficient MMR (pMMR) tumors[60, 61]. In terms of clinical outcomes, dMMR tumors exhibit higher rates of pelvic relapse, lymphatic dissemination, and primary lymph node involvement[62]. A recent systematic review noted that dMMR tumors tend to present at lower tumor stages compared to pMMR tumors, yet it also highlighted that other tumor characteristics indicative of metastatic disease are more prevalent in dMMR cases[63].

3. p53 abnormal endometrial cancer

The TP53 mutation is associated with a poor prognosis in endometrial cancer, and there is a significant correlation between this mutation and high-grade tumors, advanced stage, cervical involvement, and adnexal involvement[64, 65]. These characteristics of the tumor make them similar to type II endometrial cancer in Bokhman's classification[10].

Testing p53 IHC for representing TP53 mutation has excellent concordance[66, 67]. To simplify, there are 2 types of p53 expression: the normal or wild-type pattern and abnormal expression[68]. The normal wild-type pattern can demonstrate a considerable range of staining, from very few tumor cell nuclei being positive to the majority of nuclei exhibiting positivity, depending on the cellular differentiation state. On the other hand, abnormal expression includes 3 specific patterns: overexpression, cytoplasmic expression, and complete absence of expression[66]. However, careful consideration of the histological pattern remains a vital component of pathological diagnosis and has significant implications for clinical management.

Clinical implication

Abnormal p53 expression is detected in approximately 8-24% of endometrial cancers[24, 69]. Typically, p53 abnormalities are associated with high CNV and low TMB. The p53 expression found in older patients exhibits more aggressive features and is more prevalent in non-endometrioid histology and in more advanced stages of the disease, such as 61.3% demonstrating lymphovascular space invasion (LVSI), and 14.5% presenting with lymph node positivity[69]. In terms of prognosis, tumors with p53 abnormalities demonstrate a higher rate of cervical involvement, increased lymphatic spread, and poorer survival outcomes[71, 72].

According to the ESMO guideline from 2022, tumors with p53 abnormality are classified as high-risk carcinoma, even in early stages. These cases necessitate the adjuvant treatment with systemic chemotherapy in combination with radiotherapy[55, 56].

4. No specific molecular profile endometrial cancer

When molecular testing for endometrial cancer yields negative findings for POLE mutation, MMR, and p53, the cancer is categorized as having a no specific molecular profile (NSMP). This classification represents the most prevalent type among the 4 types identified in the TCGA classification of endometrial cancer, accounting for approximately 40% of cases. According to the ProMisE classification, the primary characteristics of NSMP include low-grade histology, a low number of mutations—indicating a low TMB—and low CNV[73]. As suggested by its name, the no specific molecular profile corresponds to a heterogeneous tumor group. The most common histology in this category is endometrioid, comprising about 70% of cases; the remaining cases include high-grade carcinoma with ambiguous morphology, clear cell carcinoma, mesonephric-like carcinoma, and carcinosarcoma.

Clinical implication

Due to its heterogeneous nature, any molecular test outside the 4 types defined in the ProMisE classification would also be categorized as NSMP.

There is also a high expression rate of estrogen and progesterone receptors—around 80%—within the NSMP group[74]. The hormonal treatment might be considered in some situations. The NSMP group is stratified as having an intermediate risk prognosis. However, this classification encompasses a wide range of diversity, meaning that management for this group remains dependent on factors such as stage, grade, and histology.

Some practical points of molecular testing for endometrial cancer

• Diagnostic or surgical samples

An initial diagnosis prior to surgical staging is crucial for surgical planning, particularly for young women who wish to preserve their ovarian function and fertility. Therefore, identifying the molecular subtype is essential for assessing the risk probability of tumor progression. Patients with p53abn tumors have been shown to have the poorest outcomes, with a progression rate or necessity for definitive therapy at 50%[64]. In contrast, patients with POLE-mutated tumors progressed or required definitive therapy in only 25% of cases, and these tumors exhibited the longest median time to progression[75, 76]. Thus, understanding risk stratification through molecular testing serves as a significant tool in treatment decision-making. Furthermore, the correlation between molecular testing results from diagnostic samples and surgical samples demonstrates good concordance[77]. This finding aligns with the FIGO 2023 recommendations, which suggest prioritizing molecular testing from diagnostic samples[78]. Not only for the pretreatment planning purposes, but also for the yield of the preserved tumor specimen quality for testing.

• Molecular testing for endometrial cancer in patient approach

The process shares similarities with genetic counseling. Nevertheless, there are several considerations as the following:

1. Conduct a thorough medical history and comprehensive physical examination of the patient.

2. Evaluate the family history and construct a pedigree.

3. Discuss the objectives of the test to optimize personalized testing, including:

- Prognosis and risk stratification for recurrence
- Identification of germline mutations
- Available treatment options: immunotherapy, hormonal therapy, and targeted therapy.

4. Examine the accuracy of the test and the treatment options that are based on molecular testing in both primary and recurrent settings.

5. In cases associated with germline mutations, genetic counseling should be initiated.

• Algorithms for molecular testing

Molecular testing with POLE sequencing is not feasible due to poor access and the high cost in the limited settings. In Thailand, the real-world situation is still facing resource limitations; only tertiary hospitals can support POLE testing, which uses next-generation sequencing analysis. To reduce the cost of the investigation, initiating the test for MMR would be a more convenient approach. There is research focusing on modified molecular testing evaluations in the northern part of Thailand, designing a cost-effective algorithm that follows the ProMisE flow[79]. Initially, MMR status was assessed using just 2 key markers: PMS2 and MSH6. This approach has the advantage not only in being conducted using IHC but also detects the dMMR, which serves as a screen for Lynch syndrome and offers the potential for treatment with immune checkpoint inhibitors.

In cases where proficient MMR is identified, it may be worthwhile considering POLE sequence testing in stages I and II to explore the possibility of de-escalating treatment.

Additionally, for molecular testing beyond the TCGA, it is important to evaluate HER2/neu expression in serous tumors and carcinosarcomas, as well as estrogen and progesterone receptor status in the NSMP group. If the POLE test results show a wild type, the p53 IHC test is then conducted (Fig. 1). Moreover, some cases may receive inadequate treatment due to a lack of molecular testing. For

example, low-grade histology in early-stage disease may lead to the omission of adjuvant therapy or the use of only brachytherapy. These findings align with recent data indicating a significantly high recurrence risk in stage I p53-abnormal low-grade endometrial cancer[80].

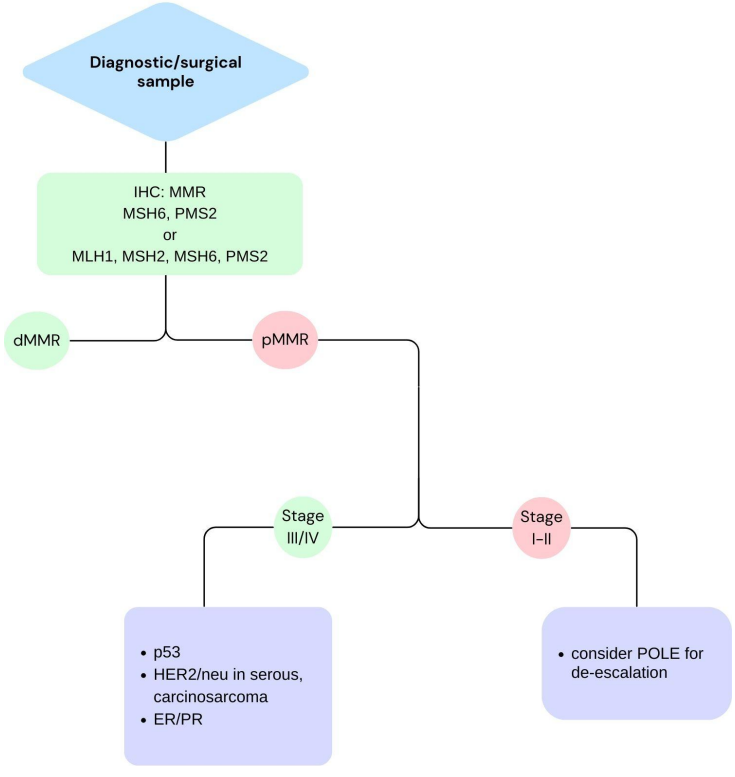

Fig. 1. Modified algorithm for molecular testing in endometrial cancer.

Conclusion

The ongoing development of the molecular testing algorithm for endometrial cancer in Thailand highlights the shift towards personalized treatment approaches. Recommendations emphasize the importance of evaluating MMR status to detect Lynch syndrome and assess potential benefits from immunotherapy. Specifically, POLE sequencing should be restricted to patients with stage I-II disease, while MMR status, p53 IHC, and hormonal receptor assessments should be conducted for all patients. Molecular testing is crucial not only for guiding surgical decisions and determining adjuvant treatment options post-surgery but also for influencing de-escalation strategies and considerations for immunotherapy.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 13-22.

OBSTETRIC

Comparison of Depression Scores between Teenagers with Unintended Pregnancy Who Underwent Medical Abortion and Those Who Underwent Delivery in Ramathibodi Hospital using the Thai Edinburgh Postnatal Depression Scale

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ABSTRACT

Objectives: The aim of this study was to compare teenagers with unintended pregnancy that terminated their pregnancy and those who delivered using the Thai Edinburgh Postnatal Depression Scale (EPDS) and determine predisposing factors for depression.

Materials and Methods: This cross-sectional study was conducted at a tertiary hospital between September 2018 and July 2019. Only data for unintended teenage pregnancies that underwent medical abortion or delivery were included. Exclusion criteria were intended pregnancy, history of major deressive disorder diagnosis, and refusal to participate. All participants completed the EPDS within 2 weeks after termination or delivery.

Results: In total, 131 teenage pregnancies were recorded over the study period. We excluded 10 intended pregnancies and one woman with history of major depressive disorder diagnosis. Sixty-five women underwent medical abortion (abortion group) and 55 underwent delivery (delivery group). Overall, there was no statistically significant difference in the total EPDS score between the two groups. There were 23 women (19.2%) with an EPDS score ≥ 11. The delivery group was more likely to have developed depression compared with the abortion group (25.4% vs 13.8%, risk ratio [RR] 0.87, 95% confidence interval [CI] 0.72-1.04). The delivery group was more likely to live with a partner than the abortion group (54.5% vs 9.2%, $p < 0.01$). Significant protective factors for postpartum depression were having family support (RR 2.26, 95%CI 1.16-3.27), continuing education (RR 1.27, 95%CI 1.07-1.51), and living with a partner (RR 1.20, 95%CI 1.03-1.41).

Conclusion: More teenagers with unintended pregnancy who delivered had postpartum depression than those who terminated their pregnancy, although the difference was not statistically significant. No family support, dropout from school, and living alone were predisposing factors for depression.

Keywords: abortion, unintended pregnancy, teenage pregnancy, postpartum depression.

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Received: 14 April 2024, **Revised:** 13 August 2024, **Accepted:** 15 August 2024

การศึกษาเปรียบเทียบระดับความซึมเศร้าระหว่างหญิงวัยรุ่นตั้งครรภ์ไม่พึงประสงที่เข้ารับการยุติการตั้งครรภ์โดยการใช้ยา และกลุ่มหญิงวัยรุ่นตั้งครรภ์ที่เข้ารับการคลอดบุตร โรงพยาบาลรามาธิบดี โดยใช้แบบสอบถาม Thai Edinburgh Postnatal Depression Scale

แมน ทองอร่าม, อภิสิทธิ์ สาราลักษณ์ ,สัญญา ภัทราชัย, คมกฤช เอี่ยมจิรกุล, ชุติมา หรุ่มเรืองวงษ์, อรวี ฉินทกานันท์

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาเปรียบเทียบระดับความซึมเศร้า Edinburgh Postnatal Depression Scale (EPDS) ระหว่างหญิงตั้งครรภ์วัยรุ่นไม่พึงประสงค์ที่เข้ารับการยุติการตั้งครรภ์ เทียบกับหญิงตั้งครรภ์วัยรุ่นที่เข้ารับการคลอดบุตร และศึกษาถึงปัจจัยเสี่ยงต่าง ๆ ที่ทำให้เกิดภาวะซึมเศร้าหลังคลอดในหญิงตั้งครรภ์ทั้งสองกลุ่มนี้*

วัสดุและวิธีการ*: การศึกษาวิจัยนี้เป็นการศึกษาเก็บข้อมูล ณ จุดเวลาใดเวลา ในหญิงตั้งครรภ์ไม่พึงประสงค์ที่โรงพยาบาลรามาธิบดี ตั้งแต่ เดือนกันยายน 2561 – เดือนกรกฎาคม 2562 โดยหญิงวัยรุ่นตั้งครรภ์ไม่พึงประสงค์ที่เข้ารับการยุติการตั้งครรภ์ หรือ เข้ารับการคลอดบุตรจะได้รับการเข้าร่วมการวิจัย ส่วนหญิงตั้งครรภ์พึงประสงค์ หญิงที่มีโรคประจำตัวทางจิตเวช หรือปฏิเสธเข้าร่วมการวิจัยจะถูกคัดออกจากการวิจัยนี้ ซึ่งผู้เข้าร่วมการวิจัยทั้งสองกลุ่ม จะได้รับการทำแบบสอบถามเพื่อประเมินภาวะซึมเศร้า EPDS ภายใน 2 สัปดาห์ หลังยุติการตั้งครรภ์ หรือ หลังคลอด*

ผลการศึกษา*: ในหญิงตั้งครรภ์วัยรุ่นทั้งหมด 131 ราย พบว่า มีจำนวน 10 รายที่เป็นการตั้งครรภ์พึงประสงค์ และ 1 ราย มีภาวะซึมเศร้ามาตั้งแต่ก่อนตั้งครรภ์แล้ว ซึ่งในทั้ง 2 กลุ่มพบว่า มีหญิงตั้งครรภ์วัยรุ่นที่เข้ารับการยุติการตั้งครรภ์ทั้งสิ้น 65 ราย และมีหญิงตั้งครรภ์วัยรุ่นที่เข้ารับการคลอดบุตรทั้งสิ้น 55 ราย โดยมีหญิงตั้งครรภ์วัยรุ่นทั้งหมด 23 ราย (ร้อยละ 19.2) ที่มีคะแนน EPDS score ≥ 11 ซึ่งมีแนวโน้มที่จะเกิดภาวะซึมเศร้าหลังคลอด และพบว่า ในกลุ่มหญิงตั้งครรภ์วัยรุ่นที่เข้า*

รับการคลอดบุตร มีแนวโน้มจะเกิดภาวะซึมเศร้าได้มากกว่ากลุ่มยุติการตั้งครรภ์ ร้อยละ 13 (ร้อยละ 25.4 เทียบกับร้อยละ 13.8, RR 0.87, 95%CI 0.721-1.039) โดยในกลุ่มที่เข้ารับการคลอดพบว่า ยังอยู่ร่วมกันกับสามีมากกว่ากลุ่มที่ยุติการตั้งครรภ์อย่างมีนัยะสำคัญ (ร้อยละ 54.5 เทียบกับ ร้อยละ 9.2, p < 0.01) และพบว่าปัจจัยส่งเสริมที่จะไม่ทำให้เกิดภาวะซึมเศร้าในหญิงตั้งครรภ์ทั้งสองกลุ่มนี้ ประกอบไปด้วย การได้รับการสนับสนุนจากครอบครัว (RR 2.26, 95%CI 1.158-3.269) ยังเรียนอยู่ในสถานศึกษา (RR 1.27, 95%CI 1.065-1.508) และการยังอยู่ร่วมกันกับสามี (RR 1.20, 95%CI 1.030-1.405)

***สรุป**: ในหญิงวัยรุ่นตั้งครรภ์ไม่พึงประสงค์ที่เข้ารับการคลอดบุตร มีแนวโน้มที่จะมีความเสี่ยงต่อภาวะซึมเศร้าหลังคลอดมากกว่าหญิงตั้งครรภ์ที่ตัดสินใจยุติการตั้งครรภ์ แต่ไม่ได้มีนัยยะสำคัญทางสถิติ และการที่ไม่ได้รับการสนับสนุนจากครอบครัว, เลิกเรียน, เลิกกับสามีของตน เป็นความเสี่ยงที่จะทำให้เกิดภาวะซึมเศร้าหลังคลอดในกลุ่มตัวอย่างนี้*

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Introduction

A common primary cause of the adverse psychological effects following pregnancy and childbirth are maternal complications, fetal anomalies, fetal deaths, and abortion[1]. Postpartum depression (PPD) is an important complication during pregnancy and the postpartum period[2]. Women with PPD may experience intense feelings of sadness, anxiety, or despair that prevent them from performing their daily tasks. PPD occurs in the perinatal period, which ranges from conception to 1 year after delivery. However, it commonly occurs within 1-3 weeks postpartum. In the same way as postabortion depression, especially unintend pregnancy, women may experience intense feelings of sadness, guilt, and anxiety, which are common in postpartum depression[3]. Unintended pregnancy is based on the World Health Organization (WHO), which defines unintended pregnancy as a pregnancy that is either mistimed and occurs earlier than desired[4]. Several factors had been proposed to be the etiologies and risk factors for psychological effects and depression after postpartum or postabortion especially unintended pregnancy[1, 5]. First, changes in hormone levels; for example, declining levels of estrogen and progesterone after delivery affect the expression of the Gamma-Aminobutyric Acid A Receptor (GABAAR) subunit in the hippocampus that may lead to mood changes among women[6]. This may also explain the mood swings in the premenstrual period. Second, women with a history of depression or being treated for depression may have an increased risk for psychological effects and depression after postpartum or postabortion. Third, emotional factors also play a role, as unplanned or unintended pregnancy can affect a woman's feelings about her unborn baby or give rise to guilt about not raising the child. Fourth, various lifestyle factors are important contributors, such as lack of family support or stress from life events. Finally, age is a major risk factor, as the risk for depression is higher in teenage pregnancy than among women in other age groups[7]. American College of Obstetricians and Gynecologists (ACOG) recommended that obstetrician-gynecologists and other obstetric care providers should screen patients for depression at least once during the perinatal period using a standardized and validated tool.

The Edinburgh Postnatal Depression Scale (EPDS) is the most frequently used tool for PPD screening, and it was also used for screening depression after abortion in many previous studies[8-10]. It consists of 10 self-reported items and takes 5-10

minutes to complete. The EPDS has been translated into more than 50 different languages. The Thai version of the EPDS has been validated in a Thai population[11], with the cutoff point reduced from 13 to 10; this resulted in sensitivity of 100%, specificity of 88%, and degree of agreement of 0.38[12]. A meta-analysis of 59 studies showed the incidence of PPD within 12 weeks postpartum was around 13%[13]. Another systematic review and meta analysis demonstrated the estimated incidence of PPD was 6.5% - 12.9%[14]. Several studies fo-cused on perinatal depression have been conducted in Thailand. The incidence of PPD in mothers who had postpartum complications in Thailand was 13.7%[15], which was similar to previous studies[14]. However, the incidence of PPD among teenage mothers rose to 25.5%[16], which confirmed teenage pregnancy was a risk factor for PPD. Interestingly, the meta-analysis revealed that the overall pooled prevalence of post-abortion depression was 34.5% and varied based on geographic location and World Health Organization (WHO) regions. Asia exhibited the greatest percentage of post-abortion depression (37.5%)[17]. Women with unintended pregnancy who undergo pregnancy termination may experience stigma, including feelings of guilt, shame, and fear of judgment from society.

In this study, teenage pregnancy was defined as pregnant women under the age of 20 years at the time their pregnancy ended. Our primary objective was to compare depression scores between teenagers with unintended pregnancy who underwent medical abortion and those who underwent delivery using the Thai version of the EPDS. The secondary outcomes were to investigate the prevalence of PPD in these two groups and clarify predisposing factors for PPD.

Materials and Methods

This cross-sectional study compared Thai EPDS scores between teenagers with unintended pregnancy who underwent medical abortion and those who underwent delivery at Ramathibodi Hospital between September 2018 and July 2019. The present study was approved by the Research Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (IRB number MURA2018/357). We included unintended teenage pregnancies which was defined as pregnant women under the age of 20 years at the time their pregnancy ended that underwent medical abortion or underwent delivery. The definition of unintended pregnancy in this study is based on the World Health Organization (WHO), which defines unintended pregnancy as a pregnancy that is either mistimed and occurs earlier than desired or unwanted and occurs when no children, or no more children, were desired at all. All participants were confirmed to be compatible with the definition. The patients who had postpartum or postabortion complications for either mother or baby were excluded from this study. The exclusion criteria were participants who refused to participate from the protocol, or had underlying psychiatric diseases. Participants were recruited from obstetrics and gynecology clinic using hospital recruitment. Participants were able to ask questions of investigators who were trained in all trial procedures. The researchers ensured that the participants meet the inclusion and exclusion criteria. After the consent form was signed at the beginning of termination of pregnancy process, participant was invited to attend as the protocol. All participants completed Thai EPDS within 2 weeks after delivery or pregnancy termination (Fig. 1). Demographic data and Thai EPDS scores were collected and analyzed. Women that had screened positive for PPD were advised to make an appointment with a psychiatrist. A higher Thai EPDS score indicated a higher level of depression.

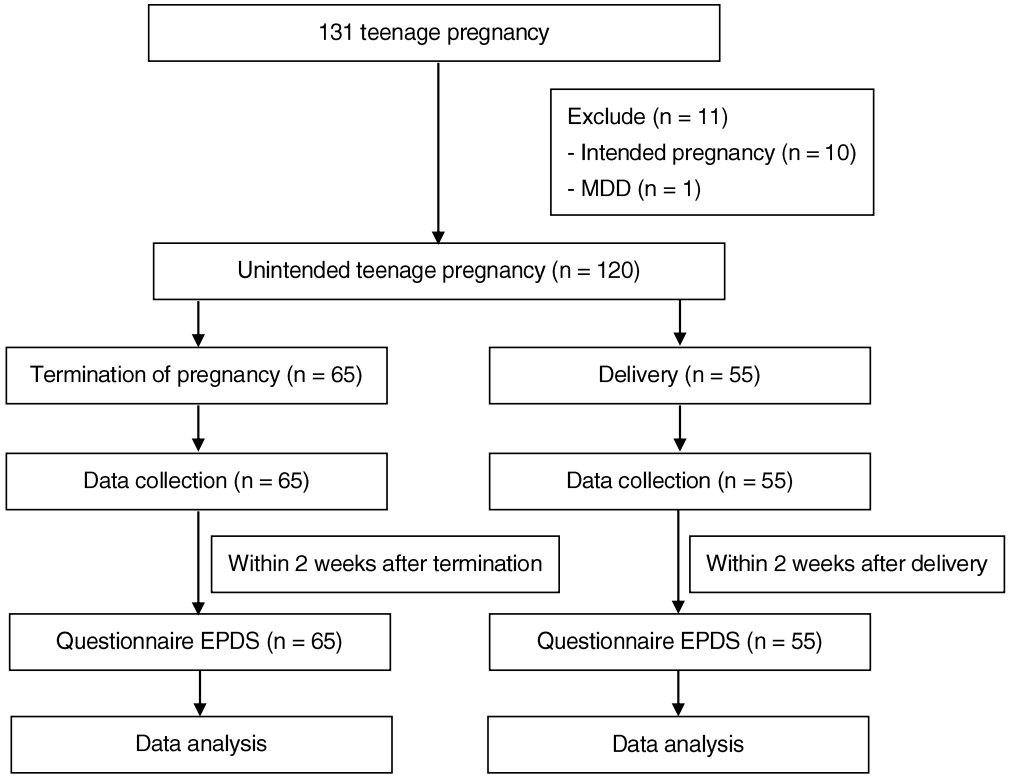
Among women who delivered, only those with a gestational age more than 36^{+6} weeks were included in this study. Any route of delivery was included (e.g., normal labor, cesarean section, forceps extraction, and vacuum extraction). In women who had a termination, the termination of pregnancy protocol started before a gestational age of 24 weeks. Women received mifepristone and then misoprostol within 24-48 hours to decrease the chance of complications[17].

Statistical analysis was performed using SPSS version 18.0.0. Quantitative data were first analyzed using percentages, means, and standard deviations,

and compared using student's t tests. We then performed chi-square tests and multivariate logistic regression analysis. The level of statistical significance was set at $p < 0.05$.

Results

Over the study period, 131 teenage pregnancies were included in this study, 10 participants were excluded because of intended pregnancy and one was excluded because of an underlying major depressive disorder. There were 65 participants in the group that terminated pregnancy (abortion group) and 55 in the delivery group; giving a total of 120 unintended teenage pregnancies. Demographic data were collected, and all participants completed the questionnaire within 2 weeks after termination or delivery (Fig. 1).



MDD: major depressive disorder, EPDS: Edinburgh postnatal depression scale

Fig. 1. Protocol flow diagram.

In both groups, participants' mean age was 18 years and that of their partners was 20 years. More than half of the participants had dropped out of school, and most were Buddhist. The mean daily income was lower in the abortion group than the delivery group (353 Baht vs 1,509 Baht). Overall, there were few married participants (none in the abortion group and 5.5% in the delivery group). The only significant difference between the two groups was living with a partner; the delivery group was more likely to live with a partner than the abortion group (54.5% vs 9.2%, $p < 0.001$). All participants reported not using illicit drugs. Two-thirds reported having family support (72.3% in the abortion group vs 65.5% in the delivery group). In terms of pregnancy-associated symptoms, the delivery group was statistically significantly more

likely to suffer from muscle pain than the abortion group (47.3% vs 21.5%, p = 0.003) (Table 1). Most participants in this study reported not using contraception (63.1% in the abortion group vs 49.1% in the delivery group). Among those that used contraception in the delivery group, oral contraceptive pills were most common, followed by condoms and the emergency pill. In contrast, emergency contraception was the most common in the abortion group followed by condoms and oral contraceptive pills.

Table 1. Participants' demographic data and clinical characteristics.

	Abortion (n = 65) n (%)	**Delivery (n = 55) n (%)**	**p value**
Age (years)*	17.60 ± 1.08	17.92 ± 1.05	0.098
Personal income per day* (Baht)	353.84 ± 1,429	1,509 ± 4,662	0.518
Partner's age (years)*	19.93 ± 2.39	20.63 ± 2.50	0.122
Being in school	31 (47.70)	25 (45.50)	0.807
Buddhist	65 (100)	51 (92.70)	0.042
Marriage certificate	0 (0)	3 (5.50)	0.093
Living with partner	6 (9.20)	30 (54.50)	< 0.001
Not use contraception	41 (63.10)	27 (49.10)	0.230
History of abortion	0 (0)	1 (1.80)	0.458
Substance use	0 (0)	0 (0)	-
Family support	47 (72.30)	36 (65.50)	0.418
Symptoms at the time of abortion (medical abortion)/delivery.			
Frequency of urine	42 (64.60)	39 (70.90)	0.463
Backache	21 (32.30)	22 (40.00)	0.381
Muscle pain	14 (21.50)	26 (47.30)	0.003
Cramp	18 (27.70)	20 (36.40)	0.309
Fatigue	20 (30.80)	25 (45.50)	0.098
Nausea	22 (33.80)	18 (32.70)	0.897

* mean ± standard deviation

In the delivery group, 91% underwent vaginal delivery and 9% underwent cesarean section because of cephalopelvic disproportion, breech presentation, or non-reassuring fetal status. Of the 55 infants, 24 were boys (43.6%) and 31 were girls (56.4%). The mean birth weight was 2,992 ± 346.71 grams. The mean time for the first stage of labor was 477.20 ± 232.63 minutes and that of the second stage was 28.54 ± 16.59 minutes. The mean blood loss was 254.54 ± 64.02 ml.

All participants in the abortion group underwent a successful medical abortion. There were no major complications. The delivery group had significantly higher mean scores on the Thai

EPDS for questions 3, 6, and 8 than the abortion group. However, there was no statistically significant difference in the total EPDS score between the two groups (Table 2).

The prevalence of PPD was 13.8% in the abortion group and 25.4% in the delivery group (RR 0.87, 95%CI 0.72–1.03). Overall, the prevalence of PPD in this study was 19.1%. The secondary outcome was predisposing factors for PPD. We found three statistically significant protective factors for PPD: family support, living with a partner, and being in school (Table 3). After controlling for possible confounding factors, the only significant risk factor for PPD was no family support (adjusted odds ratio 0.02, 95%CI 0.01–0.09, p < 0.01).

Table 2. Comparison of mean Thai Edinburgh Postnatal Depression Scale scores between the groups.

	Abortion group (mean)	Delivery group (mean)	p value
Q1: I have been able to laugh and see the funny side of things	0.46	0.58	0.387
Q2: I have looked forward with enjoyment to things	0.52	0.61	0.511
Q3: I have blamed myself unnecessarily when things went wrong	0.58	0.85	0.049
Q4: I have been anxious or worried for no good reason	0.44	0.69	0.103
Q5: I have felt scared or panicky for no very good reason	0.35	0.45	0.403
Q6: Things have been getting on top of me	0.46	0.80	0.024
Q7: I have been so unhappy that I have had difficulty sleeping	0.66	0.69	0.840
Q8: I have felt sad or miserable	0.35	0.61	0.036
Q9: I have been so unhappy that I have been crying	0.38	0.58	0.117
Q10: The thought of harming myself has occurred to me	0.27	0.16	0.220
Total score	4.49	6.05	0.067

Table 3. Factors associated with postpartum depression.

	Screen positive n (%)	Screen negative n (%)	RR (95%CI)	p value
With family support	2 (2.40)	81 (97.6)	2.26 (1.16 - 3.27)	< 0.001
Living with partner	3 (8.30)	33 (91.7)	1.20 (1.03 - 1.40)	0.048
Being in school	5 (8.9)	51 (91.1)	1.27 (1.07 - 1.51)	0.008

CI: confidence interval, RR: risk ratio.

Discussion

In a study examining the EPDS scores of 120 women, 65 underwent medical abortion (abortion group) and 55 underwent delivery (delivery group). Among these women, 23 (19.2%) had an EPDS score of 11 or higher, indicating potential depression. The delivery group exhibited a higher prevalence of depression compared to the abortion group (25.4% vs 13.8%). Additionally, the delivery group was more likely to live with a partner (54.5% vs 9.2%). Significant protective factors against postpartum depression included having family support, continuing education, and living with a partner.

Teenage pregnancy is a complicated problem in many countries, particularly in developing countries such as Thailand. The prevalence of teenage pregnancy in Thailand was 14.2% - 16.9% in 2012 - 2016. The Thai government issued the "Adolescent Pregnancy Bill" in 2016 to prevent unintended pregnancy and reduce adolescent childbearing; however, the number of teenage pregnancies has increased. Many factors are related to teenage pregnancy, including personal factors, family factors, peer pressure, social issues, and environment problems. Our study suggested that most unintended pregnancies resulted from not using contraception. Correcting misconceptions and attitudes about sex and contraceptive use in this age group should be addressed. This may be an effective method to improve adolescents' sexual health.

Our study showed that less than 10% of those in the abortion group still lived with their partner. In contrast, more than 50% of the delivery group lived with their partners. This suggested that being a single mother might have impacted the decision to terminate their pregnancy.

Teenage pregnancy has major impact on the physical and mental health of affected adolescents. It is not only teenage mothers that are affected by pregnancy, as it also affects newborn babies, families of adolescent mothers and society. PPD is one of the most common psychiatric problems among teenagers that fall pregnant. The prevalence of PPD in the delivery group in this study was 25.4%. This result was comparable with a previous study[10] that reported a prevalence of PPD among unintended teenage pregnancy of 29.9% in the first 2 weeks postpartum and 25.5% after 4-6 weeks postpartum. Known risk factors for PPD include young age, a woman's prenatal psychopathological characteristics, level of prenatal attachment to child, quality of the woman's romantic relationship, and clinical delivery difficulties[18]. For women that had an abortion, the risk factors for PPD included a younger age, low education level, an older gestational age at abortion, being single, an assisted mode of conception and prior miscarriage[19]. Unintended teenage pregnancies without family support had a 2.3 times higher risk for PPD than those with family support (RR 2.26, 95%CI 1.16–3.27). The other two significant protective factors for PPD in this study were living with a partner and being in school. These findings emphasized that support from a partner, friends, and family play important roles in preventing PPD.

The prevalence of PPD was slightly higher in the delivery group compared with the abortion group (25.4% vs 13.8%); however, the difference was not statistically significant. This may be explained by both physical and psychological aspects. The decrease of estrogen and progesterone may impact depressive mood; therefore, the delivery group tended to show more impact than the abortion group. A systematic review demonstrated that inadequate support from significant others was a major factor for PPD[20]. Our study showed similar results. In addition, the delivery group demonstrated lower family support than the abortion group.

Mothers need support from health professionals because PPD has a major influence on the well-being of mothers and children. Therefore, health professionals should pay attention to pregnant teenagers who do not have family support, have quit school, or separated from their partners. For prevention of PPD, we should screen all pregnant women who undergo hospital-based delivery.

The strength of this study was that we used a prospective cohort design that had no recall or selection bias. We investigated a specific population; this was a pioneering study in Thailand about PPD in a postabortion group. A limitation of this study was that it was only a single site study and was conducted in a tertiary hospital; therefore, the results may not be generalizable to rural areas or other settings.

Conclusion

More teenagers with unintended pregnancy who delivered had PPD than those who terminated their pregnancy, although this finding was not statistically significant. No family support, dropout from school and living alone were predisposing factors for PPD.

Acknowledgments

The authors would like to offer special thanks to Mrs. Umaporn Udomsubpayakul for guidance on statistical analysis. We also thank Audrey Holmes, MA, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 23-34.

OBSTETRICS

Effect of Hemming Stitch Closure of Peritoneum at Cesarean Section on Adhesions: A Randomized Controlled Trial

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ABSTRACT

Objectives: To study the effect of Hemming stitch closure of the peritoneum at cesarean section on intra-abdominal adhesions and compare postoperative adhesion formation rate between the Hemming stitch closure group, the simple closure group, and the non-closure group.

Materials and Methods: A prospective randomized controlled trial was conducted at Phon Hospital with 240 primiparous patients carrying full-term single fetuses, delivered by cesarean section between May 2017 and January 2020. They were randomized into 3 groups: 80 primiparous patients in the non-closure group, 80 primiparous patients in the simple closure group, and 80 primiparous patients in the Hemming stitch closure group. Between July 2019 and February 2024, 146 patients (46 cases in the non-closure group, 52 cases in the simple closure group, and 48 cases in the Hemming stitch closure group) returned for subsequent cesarean section. Data on adhesion formation were collected and analyzed using the SPSS program.

Results: The total adhesion formation rates in the Hemming stitch closure group, simple closure group, and non-closure group were 10.4%, 48.1%, and 58.7%, respectively. The severe adhesion formation rates were 4.2%, 15.4%, and 39.1%, respectively. The total adhesion formation rates and severe adhesion formation rate in the Hemming stitch closure group were statistically significantly lower than in the simple closure group and non-closure group ($p < 0.05$).

Conclusion: Hemming stitch closure of the peritoneum at cesarean section reduces both the overall adhesion formation rate and the rate of severe adhesion. The author recommends using Hemming stitch closure of the peritoneum in cesarean section procedures to effectively reduce the adhesion formation rate.

Keywords: hemming stitch closure, peritoneum closure, non-closure, cesarean section, adhesion.

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Received: 5 May 2024, **Revised:** 30 October 2024, **Accepted:** 13 November 2024

ผลของการเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้องต่อการเกิดพังผืดหลังการผ่าตัดคลอดทางหน้าท้อง: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

ประพจน์ เนติโรจนกุล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้องต่อการเกิดพังผืดในช่องท้องหลังการผ่าตัดคลอด และเพื่อเปรียบเทียบอัตราการเกิดพังผืดหลังการผ่าตัดคลอดระหว่างกลุ่มที่ได้รับการเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง กลุ่มที่ได้รับการเย็บปิดเยื่อบุช่องท้องด้วยวิธีดั้งเดิมและกลุ่มที่ไม่ได้เย็บปิดเยื่อบุช่องท้อง*

วัสดุและวิธีการ: *การวิจัยแบบสุ่มและมีกลุ่มควบคุมนี้ เป็นการวิจัยไปข้างหน้าซึ่งดำเนินการที่โรงพยาบาลพล ในหญิงตั้งครรภ์เดี่ยว และครรภ์แรกที่มาคลอดบุตรโดยมีข้อบ่งชี้การผ่าตัดคลอดทางหน้าท้องเป็นครั้งแรก ในระหว่าง พฤษภาคม 2560 ถึง มกราคม 2563 รวมทั้งหมด 240 คน แล้วแบ่งเป็น 3 กลุ่มโดยวิธีสุ่ม ดังนี้ กลุ่มที่ 1 ได้รับการผ่าตัดคลอดโดยไม่เย็บปิดเยื่อบุช่องท้อง 80 คน กลุ่มที่ 2 ได้รับการผ่าตัดคลอดโดยเย็บปิดเยื่อบุช่องท้องด้วยวิธีดั้งเดิม 80 คน และกลุ่มที่ 3 ได้รับการผ่าตัดคลอดโดยเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง 80 คน เมื่อทำการติดตามผลตั้งแต่กรกฎาคม 2562 ถึง กุมภาพันธ์ 2567 มีผู้ป่วย 146 คนกลับมาผ่าตัดคลอดซ้ำ เป็นผู้ป่วยในกลุ่มที่ 1 ไม่เย็บปิดเยื่อบุช่องท้อง 46 คน กลุ่มที่ 2 เย็บปิดเยื่อบุช่องท้องด้วยวิธีดั้งเดิม 52 คน และกลุ่มที่ 3 เย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง 48 คน จึงทำการเก็บรวบรวมข้อมูลการเกิดพังผืดที่พบ และวิเคราะห์ข้อมูลโดยใช้โปรแกรม SPSS*

ผลการศึกษา: *ผู้ป่วยกลุ่มที่เย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง ผู้ป่วยกลุ่มที่เย็บปิดเยื่อบุช่องท้องด้วยวิธีดั้งเดิม และผู้ป่วยกลุ่มที่ไม่เย็บปิดเยื่อบุช่องท้อง มีอัตราการเกิดพังผืดรวม ร้อยละ 10.4 ร้อยละ 48.1 และร้อยละ 58.7 ตามลำดับ และมีอัตราการเกิดพังผืดชนิดหนา ร้อยละ 4.2 ร้อยละ 15.4 และร้อยละ 39.1 ตามลำดับ ผู้ป่วยกลุ่มที่เย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง มีอัตราการเกิดพังผืดรวมและมีอัตราการเกิดพังผืดชนิดหนาน้อยกว่า กลุ่มที่เย็บปิดเยื่อบุช่องท้องด้วยวิธีดั้งเดิม และผู้ป่วยกลุ่มที่ไม่เย็บปิดเยื่อบุช่องท้องอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$)*

สรุป: *การเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้องสามารถลดทั้งอัตราการเกิดพังผืดรวมและอัตราการเกิดพังผืดชนิดหนาหลังการผ่าตัดคลอดได้ ผู้วิจัยขอแนะนำให้ใช้วิธีการเย็บปิดเยื่อบุช่องท้องด้วยวิธีมิ้มขอบแผลไว้ด้านนอกช่องเยื่อบุช่องท้อง (Hemming stitch closure) ในการผ่าตัดคลอดเพื่อลดอัตราการเกิดพังผืดในช่องท้องได้อย่างมีประสิทธิภาพ*

คำสำคัญ: *วิธีมิ้มขอบแผล, การเย็บปิดเยื่อบุช่องท้อง, การไม่เย็บปิดเยื่อบุช่องท้อง, การผ่าตัดคลอดทางหน้าท้อง, การเกิดพังผืด*

Introduction

Currently, worldwide, including in Thailand, cesarean sections are being performed at a higher rate. Cesarean section is the most common major abdominal surgery performed on women of reproductive age[1-3]. Abdominal adhesions from the tissue repair process are the most common consequence after abdominal surgery. Therefore, cesarean section can cause postoperative adhesions that may lead to bowel obstruction, chronic pelvic pain, and female infertility. Additionally, these adhesions can complicate repeat cesarean sections, delay the delivery of infants, and cause injury to abdominal organs such as the intestines and bladder[4-7].

From past to present, many studies on the effects of closure and non-closure of the peritoneum at cesarean sections have shown that non-closure does not cause harm although, it does not restore the integrity of the abdominal anatomy. Currently, there are difference techniques for peritoneum closure in cesarean sections, including: 1. Non-closure (the peritoneum is left open and not sutured), 2. Parietal peritoneum closure (only the parietal peritoneum is closed), 3. Visceral peritoneum closure (only the visceral peritoneum is closed) and 4. Both parietal and visceral peritoneum closure[8]. Non-closure of peritoneum has several advantages during surgery and in short-term postoperative outcomes such as operation time, pain, and analgesia requirement[6, 9-12]. However, studies on the long-term outcomes of postoperative adhesions are varied and inconclusive. Therefore, the debate between the closure and non-closure of the peritoneum remains controversial among obstetricians and gynecologists[13-16].

Peritoneum histology consists of a single layer of mesothelial cells with an underlying supporting layer of highly vascularized loose connective tissue. The luminal surface of mesothelial cells is covered with microvilli. The proteins and serosal fluid trapped by microvilli provide a slippery, non-adhesive surface for internal organs to slide past one another (Fig. 1)[17]. Following surgery, blood and inflammatory exudate (a precursor of fibrin matrix formation) still leak from the cut edges of the peritoneum into the peritoneal cavity for a few hours. If the fibrin matrix formed in the peritoneal cavity is not completely lysed, fibroblastic proliferation may occur within them causing adhesion formation[7, 18-20]. With Hemming stitch closure of the peritoneum, both sides of the cut edges of parietal and visceral peritoneum are folded (hemmed) outside the peritoneal cavity. Therefore, blood and inflammatory exudate from the cut edges cannot enter the peritoneal cavity, and the healing process of the cut edges occurs outside the peritoneal cavity. The peritoneal cavity immediately restores its normal surface anatomy, fully covered with mesothelial cells to prevent adhesion formation.

The author hypothesized that Hemming stitch closure of the peritoneum may reduce the adhesion formation rate in cesarean sections by these mechanisms. This research was conducted to study the effect of Hemming stitch closure of the peritoneum during cesarean sections on intra-abdominal adhesions and compare the adhesion formation rate between Hemming stitch closure, simple closure, and non-closure groups.

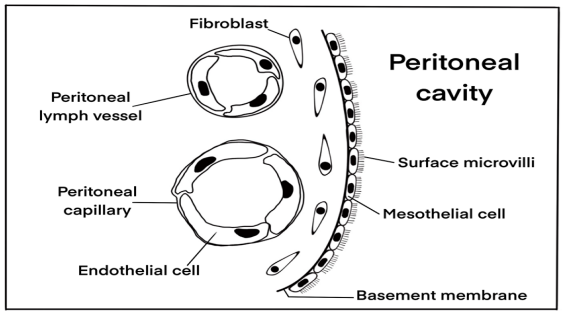

Fig. 1. Histology of the Peritoneum.

Materials and Methods

This prospective randomized controlled trial was conducted at Phon Hospital in Khon Kaen, Thailand. It was approved by the Research Ethics Committee of Phon Hospital and written informed consents were obtained from primiparous patients who met the inclusion criteria. The participants were primiparous patients aged 18-35 years with a full-term single fetus, delivered by cesarean section without any exclusion criteria (e.g. those who wanted sterilization with surgery, had adhesions found during surgery, or declined to participate).

The study was a clinical trial comparing the effects of non-closure, simple closure, and Hemming stitch closure of the visceral and parietal peritoneum on adhesion formation assessed at a subsequent cesarean section. Out of the 764 women undergoing primary cesarean section between May 2017 and January 2020, 240 primiparous patients consented to participate. They were randomly allocated into three groups using computer software-generated random sequences: 80 in the non-closure group, 80 in the simple closure group and 80 in the Hemming stitch closure group. Standard techniques were performed in all operations. The choice of anesthesia was made by the anesthesiologist independently of the treatment group. The surgeries were performed by the researcher wearing powder-free gloves. The abdomen was accessed through a Pfannenstiel incision. A transverse lower uterine segment incision was closed with two layers of continuous chromic catgut No. 1 suture with in situ uterine repair to prevent the visceral peritoneum from losing moisture. In the non-closure group, both the visceral and parietal peritoneum were left unsutured. In the simple closure group and Hemming stitch closure group, both the visceral and parietal peritoneum were closed using continuous suture patterns with simple continuous stitch and continuous hemming stitch, respectively, using chromic catgut No. 2-0 (Fig. 2). In each group, the rectus muscle reapproximation was closed with chromic catgut No. 2-0. The rectus sheath was closed with a simple continuous stitch using polyglactin (Vicryl) No. 1. The subcutaneous tissue was approximated with interrupted sutures using chromic catgut No. 2-0, followed by skin closure with a running subcuticular suture using polyglycolic acid (Dexon) No. 4-0. All patients received intraoperative prophylactic intravenous cefazolin 2 grams.

Between July 2019 and February 2024, a total of 146 patients returned for subsequent cesarean section, with 46 cases in the non-closure group, 52 cases in the simple closure group, and 48 cases in the Hemming stitch closure group. The adhesions are defined as bands of fibrous scar tissue that form on organs in the abdomen causing organs to stick to one another or to the wall of the abdomen[21]. The author was the sole doctor to perform both the initial and repeat cesarean sections. The study was a double-blind study. Participants were unaware of which treatment group they were assigned to, and the surgeon was blinded to the patient allocation when evaluating outcomes during repeat cesarean sections. The circulating nurse recorded the presence of adhesions using an adhesion record form along with the patient's identification number. If a patient had multiple sites of mixed mild and severe adhesions, the circulating nurse would only record on the most severe adhesion site. The patient's identification number would later be translated to the results of each treatment group.

Patients subsequently returning for a repeat cesarean section were evaluated intraoperatively for the presence of adhesions at various sites: abdominal wall to uterus, abdominal wall to bladder, abdominal wall to bowel, uterus to bladder, abdominal wall to omentum and uterus to omentum. Data on adhesion formation was collected. The severity of adhesions was categorized into mild adhesions (thin, clear, soft, and flexible adhesion, which can be removed with fingers) and severe adhesions (dense, tough, and hard adhesion, scissors are needed for cutting). If a single adhesion had both mild and severe components, it was classified as severe. The time from skin incision to finish operation was recorded. Postoperative fever

was defined as a temperature higher than 38°C on two consecutive postoperative days or higher than 39°C on any postoperative day. The sample size was calculated based on the primary outcome measure, which was the presence of adhesions. A pilot study of 60 participants, with 20 primipara patients in each group. After 12 cases returned for a repeat cesarean section in each group, it was found that the adhesion rates for non-closure, simple closure, and Hemming stitch closure were 58%, 50%, and 17%, respectively. The sample size was calculated for a 33% reduction in the adhesion rate (the difference in adhesion rate between simple closure and Hemming stitch closure). The minimum sample size needed was 30 patients in each group, with an alpha of 0.05 and a power of 80. The sample size in this study was set to 40 in each group. Assuming a dropout rate of 50% the participants are set to 80 in each group. Thus, the total participant is 240 primipara patients.

The data was analyzed using the SPSS program to calculate the mean, standard deviation, frequency, and percentage. The means of characteristics between more than two groups were analyzed using an F-test (one way analysis of variance: one way ANOVA) and the comparison of adhesion formation rates between groups was analyzed using a chi-square test or Fisher's exact test with a power of 95%.

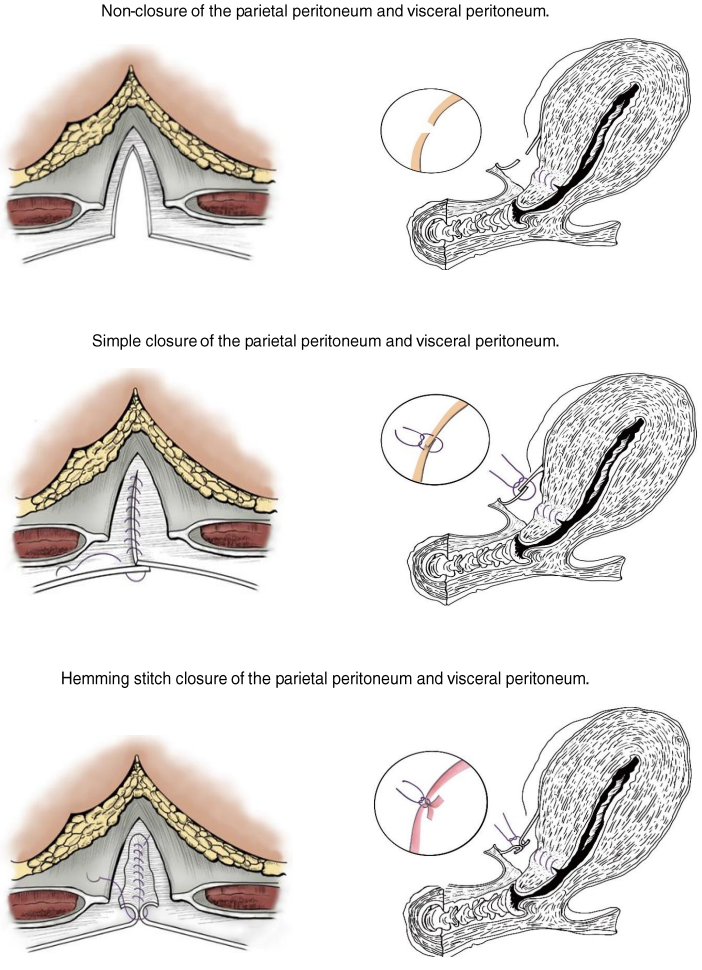

Fig. 2. Anatomical views of non-closure, simple closure and Hemming stitch closure.

Results

Of the 764 women undergoing primary cesarean section, 240 primipara patients were randomly allocated into 3 groups: 80 cases in the non-closure group, 80 cases in the simple closure group, and 80 cases in the Hemming stitch closure group. In total, 146 patients (46 in the non-closure group, 52 in the simple closure group, and 48 in the Hemming stitch closure group) returned for subsequent cesarean section to be evaluated for adhesion (Fig. 3). The characteristics of primipara patients randomized to non-closure, simple closure, and Hemming stitch closure of the peritoneum are described in Table 1. The three groups did not significantly differ in age, weight, indications for cesarean section, postoperative fever, or duration of hospitalization. However, the operation time in the non-closure group was statistically significantly shorter than in the other groups, while the operation time did not significantly differ between the simple closure group and the Hemming stitch closure group.

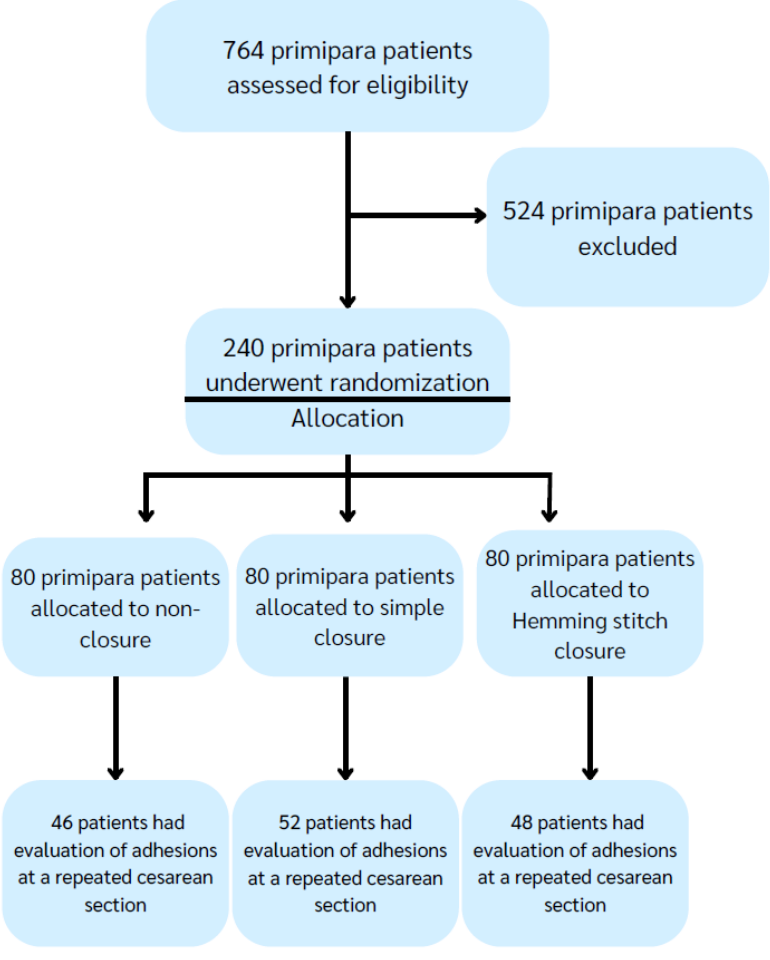

Fig. 3. Flow chart of the study.

Table 1. Characteristics of primiparous patients randomized to non-closure, simple closure, and Hemming stitch closure of the peritoneum.

Characteristics	Non-closure (n = 46)	Simple closure (n = 52)	Hemming stitch closure (n = 48)	p value
Mean age (years)	25.8 ± 3.5	25.5 ± 3.4	26.0 ± 3.0	0.781
Mean weight (kgs)	69.1 ± 7.6	69.3 ± 8.6	70.1 ± 8.2	0.827
No. of patients with indications for cesarean section				
- Labor dystocia	36 (78.3%)	39 (75.0%)	36 (75.0%)	0.838
- Fetal distress	7 (15.2%)	9 (17.3%)	7 (14.6%)	
- Breech/transverse presentation	3 (6.5%)	2 (3.85%)	4 (8.3%)	
- Placenta previa	0 (0.0%)	2 (3.85%)	1 (2.1%)	
Mean operation time (minutes)	45.0 ± 6.0	51.8 ± 5.1	53.7 ± 4.6	< 0.001
Compare the mean operation time between groups (minutes)	45.0 ± 6.0	51.8 ± 5.1	-	< 0.001
	45.0 ± 6.0	-	53.7 ± 4.6	< 0.001
	-	51.8 ± 5.1	53.7 ± 4.6	0.084
No. of patients with postoperative fever (BT > 38°C)				
- Present	4 (8.7%)	2 (3.8%)	4 (8.3%)	0.564
- Not present	42 (91.3%)	50 (96.2%)	44 (91.7%)	
Mean duration of hospitalization (days)	3.1 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	0.547

BT: body temperature

146 patients were assessed for the presence and severity of adhesions, including the mean time to delivery at repeated cesarean section (Table 2, 3). The total adhesion formation rates in the Hemming stitch closure group, simple closure group, and non-closure group were 10.4%, 48.1%, and 58.7%, respectively. Therefore, the total adhesion formation rate in the Hemming stitch closure group was statistically significantly lower than in the simple closure group and non-closure group ($p < 0.05$). Additionally, the severe adhesion rates in the Hemming stitch closure group, simple closure group, and non-closure group were 4.2%, 15.4%, and 39.1%, respectively. The severe adhesion rate in the Hemming stitch closure group was statistically significantly lower than simple closure group and non-closure group ($p < 0.05$). It was also shown that the severe adhesion rate in the non-closure group was statistically significantly higher than in the simple closure group ($p < 0.05$). The Hemming stitch closure group had the shortest mean time to deliver during repeat cesarean sections, which was statistically significantly shorter than both the simple closure and non-closure groups (9.02 min, 10.46 min, and 12.13 min, respectively).

Table 2. Adhesion formation in the non-closure group, simple closure group, and Hemming stitch closure group.

Adhesion formation	Non-closure (n = 46)	Simple closure (n = 52)	Hemming stitch closure (n = 48)	p value
No. of patients with presence of adhesion				
- Not present	19 (41.3%)	27 (51.9%)	43 (89.6%)	< 0.001
- Present	27 (58.7%)	25 (48.1%)	5 (10.4%)	
Compare the adhesion formation rate between groups (%)	27 (58.7%)	25 (48.1%)	-	0.317
	27 (58.7%)	-	5 (10.4%)	< 0.001
	-	25 (48.1%)	5 (10.4%)	< 0.001

Table 3. Severity of adhesion and the mean time to deliver in the non-closure group, simple closure group, and Hemming stitch closure group.

Severity of adhesion	Non-closure (n = 46)	Simple closure (n = 52)	Hemming stitch closure (n = 48)	p value
No. of patients with presence of adhesion				
- Not present	19 (41.3%)	27 (51.9%)	43 (89.6%)	< 0.001
- Mild adhesion*	9 (19.6%)	17 (32.7%)	3 (6.2%)	
- Severe adhesion**	18 (39.1%)	8 (15.4%)	2 (4.2%)	
Compare the severe adhesion rate between groups (%)	18 (39.1%)	8 (15.4%)	-	0.025
	18 (39.1%)	-	2 (4.2%)	< 0.001
	-	8 (15.4%)	2 (4.2%)	< 0.001
Mean time to delivery (minutes)	12.13 ± 3.84	10.46 ± 2.45	9.02 ± 1.04	< 0.001
Compare the mean time to delivery between groups (minutes)	12.13 ± 3.84	10.46 ± 2.45	-	0.002
	12.13 ± 3.84	-	9.02 ± 1.04	< 0.001
	-	10.46 ± 2.45	9.02 ± 1.04	0.008

Mild adhesions*: thin, clear, soft, and flexible adhesion, could be removed with fingers.
Severe adhesions**: dense, tough, and hard adhesion, scissors were needed for cutting.

Table 4 shows the site and severity of adhesion in all 57 patients with adhesion formation. It revealed that the most common site of adhesion was from the abdominal wall to the uterus (50.88%). This site was also the most common location of adhesion in the 28 patients with severe adhesion (71.4%).

Table 4. Site and severity of adhesion in the non-closure group, simple closure group, and Hemming stitch closure group with the presence of adhesion formation.

Severity of adhesion	Non-closure (n = 27)		Simple closure (n = 25)		Hemming stitch Closure (n = 5)		Severity of adhesion		Total (n = 57)
	Mild adhesion	Severe adhesion	Mild adhesion	Severe adhesion	Mild adhesion	Severe adhesion	Mild adhesion (n = 29)	Severe adhesion (n = 28)	
No. of patients with presence of adhesion									
- Abdominal wall to uterus	4	11	5	7	0	2	9 (31.0%)	20 (71.4%)	29 (50.88%)
- Abdominal wall to bladder	1	0	2	0	0	0	3 (10.3%)	0 (0.0%)	3 (5.26%)
- Abdominal wall to bowel	0	1	0	0	0	0	0 (0.0%)	1 (3.6%)	1 (1.75%)
- Uterus to bladder	0	1	1	0	0	0	1 (3.5%)	1 (3.6%)	2 (3.51%)
- Abdominal wall to omentum	2	3	6	0	2	0	10 (34.5%)	3 (10.7%)	13 (22.81%)
- Uterus to omentum	2	2	3	1	1	0	6 (20.7%)	3 (10.7%)	9 (15.79%)

Discussion

From past to present, the studies and the Cochrane Collaboration® review have shown that closure and non-closure of the peritoneum at cesarean section has no significant difference on intra-abdominal adhesion rate, in addition the non-closure reduces surgery time about 6 minutes and no harm was found, therefore many surgeons omit peritoneal closure due to insufficient evidence of benefit to justify the additional time and use of suture material necessary for peritoneal closure[16, 22].

At the present, there is no conclusion between closure and non-closure of the peritoneum about the better method in reducing adhesions because the results of studies are different. This has remained a controversial issue among the obstetricians and gynecologists for decades[23-26]. Most recent studies on the cesarean section procedure have focused on the short-term morbidity of closure versus non-closure of the peritoneum or closure types of the anterior abdominal wall layers in cesarean section. This focus was due to the fact that it takes less time to follow-up on the results, and the finding showed no significant impact on postoperative analgesic usage and short-term morbidity[27-28]. However, the clinical benefits on short-term morbidity are typically small when compare to the long-term morbidity such as adhesion that can lead to significant healthcare costs due to the complications they cause, particularly in terms of additional surgeries, hospital readmissions, and

longterm treatments[29]. In July 2016 the CORONIS trial a large, international clinical study designed to investigate the outcomes of different surgical techniques used during a cesarean section reported outcomes at the 3 year follow-up. Despite the large size of this trial, they did not find any technique that resulted in improved outcomes[30].

Until now, this is the first study that identified the effect of Hemming stitch closure of the peritoneum and this study showed that the total adhesion formation rate in non-closure group was slightly higher than simple closure group (58.7% vs 48.1%) but it is not statistically significant (p = 0.317) similar to previous studies[23-24]. However, using a Hemming stitch closure of the visceral and parietal peritoneum during cesarean section could reduce the overall adhesion rate by approximately five times compared to simple closure or non-closure of the peritoneum. The severe adhesion rate could be reduced by about four times when compared to the simple closure group and approximately nine times when compared to the non-closure group. Hemming stitch closure of the peritoneum may provide a solution to this controversial issue. Because this study was a double-blinded randomized controlled trial, it is the most reliable type of study. In this research the author was the only surgeon who performs surgery, so the quality of surgery was more consistent than many doctors because not all surgeons were equally skilled. The limitation of this study was that it was a long-term study with a high dropout rate (about 40%), making it hard to obtain a large sample size.

Cesarean section is the most commonly performed abdominal surgery in the world, with approximately 30 million mothers undergoing the procedure each year. If this new method is used as a standard procedure, it can prevent many patients from experiencing adhesions after cesarean section, who may suffer from the long-term effects of intra-abdominal adhesions such as intestinal obstruction, chronic pelvic pain, and infertility. Additionally, performing a subsequent cesarean section is easier, reduces the risk of injury to abdominal organs, decreases surgery time, and lowers costs.

The Hemming stitch closure is a new suturing technique that is quick and harmless, taking no more time than traditional simple continuous sutures. Surgeons can easily understand and implement this method, as it does not require any additional equipment, making it accessible to all pregnant women worldwide who require a cesarean section.

The Hemming stitch closure of the peritoneum offer a new perspective on how to close the peritoneum to achieve maximum effectiveness in preventing adhesion formation. The result of this study may change the way surgeons perform peritoneal closure in the future, and recommendations to omit peritoneal closure from many institutes may be called into question. The practice of non-closure of the peritoneum during cesarean delivery may become contraindicated in the future.

The Hemming stitch closure can also be applied to almost all intra-abdominal surgeries, including appendectomy, intestinal surgery, laparoscopic port site closure, and more. If this new method of closing the peritoneum can reduce adhesions after a cesarean section, it may also decrease abdominal adhesions resulting from other intra-abdominal surgeries. However, further research is needed to confirm the effects of Hemming stitch closure on the peritoneum in other intra-abdominal surgeries.

Conclusion

This study showed that Hemming stitch closure of the peritoneum at cesarean section reduces both the overall adhesion formation rate and the rate of severe adhesion. The author recommends using Hemming stitch closure of the peritoneum in cesarean section procedures to effectively reduce the adhesion formation rate.

Potential conflicts of interest

The author declares no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 35-43.

OBSTETRICS

Rate of Large for Gestational Age Newborns in Pregnant Women with Excessive Gestational Weight Gain

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ABSTRACT

Objectives: To compare the rate of large for gestational age (LGA) newborns between pregnant women with excessive weight gain (EWG) and appropriate weight gain (AWG)

Materials and Methods: A retrospective cohort study was conducted on pregnant women who delivered term singleton newborns between July 2020 and December 2021 at Maharaj Nakorn Chiang Mai Hospital. Pregnant women were classified as EWG and AWG regarding their pre-pregnancy body mass index (BMI) and gestational weight gain (GWG). LGA newborn was defined as birth weight > the 90th percentile for gestational age. Rates of LGA newborns, neonatal birth weight, pre-pregnancy BMI, and maternal and perinatal complications were compared between EWG and AWG groups.

Results: There were 23.4%, 59.9%, and 16.7% of 1,182 pregnant women who had EWG, AWG, and poor weight gain (PWG), respectively. The rate of LGA newborns in the EWG group was statistically higher than in the AWG group (5.8% vs 2.8%, $p = 0.026$). Pregnant women in the EWG group had statistically higher neonatal birth weight (3,240 gm vs 3,080 gm, $p < 0.001$) and higher pre-pregnancy BMI (25.1 kg/m^2 vs 22.0 kg/m^2, $p < 0.001$) than in AWG group. Logistic regression analysis showed that obesity and nulliparity were the independent risk factors for LGA newborns.

Conclusion: EWG was associated with a higher rate of LGA in newborns and was likely to occur in women with higher pre-pregnancy BMI and nulliparity. This study emphasizes the importance of preconception counseling and pregnancy education on nutrition and weight gain.

Keywords: gestational weight gain, excessive weight gain, large for gestational age, macrosomia, neonatal birth weight.

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Received: 21 May 2024, **Revised:** 24 September 2024, **Accepted:** 2 October 2024

อัตราการเกิดภาวะทารกแรกคลอดน้ำหนักเกินในสตรีตั้งครรภ์ที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์

หาญณรงศ์ ซูพูล, เฟื่องลดา ทองประเสริฐ

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการเกิดภาวะทารกแรกคลอดน้ำหนักเกินในสตรีตั้งครรภ์ที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์กับสตรีตั้งครรภ์ที่มีน้ำหนักตัวเพิ่มขึ้นตามเกณฑ์*

วัสดุและวิธีการ: *เก็บรวบรวมข้อมูลย้อนหลังของสตรีตั้งครรภ์เดี่ยวอายุครรภ์มากกว่าหรือเท่ากับ 37 สัปดาห์ขึ้นไป ที่มาคลอด ณ โรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่เดือนกรกฎาคม พ.ศ. 2563 ถึง เดือนธันวาคม พ.ศ. 2564 โดยสตรีตั้งครรภ์ถูกแบ่งเป็น 2 กลุ่ม อ้างอิงตามเกณฑ์มาตรฐานน้ำหนักตัวของสตรีตั้งครรภ์ที่ควรเพิ่มขึ้นของคนไทย ได้แก่ กลุ่มที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์ และน้ำหนักตัวเพิ่มขึ้นตามเกณฑ์ขณะตั้งครรภ์ และนำมาเปรียบเทียบอัตราการเกิดภาวะทารกแรกคลอดน้ำหนักเกินซึ่งหมายถึงทารกที่มีน้ำหนักตัวแรกคลอดมากกว่าหรือเท่ากับเปอร์เซ็นไทล์ที่ 90 ของอายุครรภ์นั้นๆ*

ผลการศึกษา: *สตรีตั้งครรภ์เดี่ยวที่คลอดครบกำหนดทั้งหมดจำนวน 1,182 คน แบ่งเป็นกลุ่มที่มีน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์ น้ำหนักเพิ่มขึ้นตามเกณฑ์ และน้ำหนักเพิ่มขึ้นน้อยกว่าเกณฑ์ ร้อยละ 23.4, 59.9 และ 16.7 ตามลำดับ อัตราการเกิดภาวะทารกแรกคลอดน้ำหนักเกินในกลุ่มที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์สูงกว่าในกลุ่มที่มีภาวะน้ำหนักเพิ่มขึ้นตามเกณฑ์อย่างมีนัยสำคัญทางสถิติ (ร้อยละ 5.8 กับ ร้อยละ 2.8, p = 0.026) น้ำหนักทารกแรกคลอดในกลุ่มที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์มากกว่าในกลุ่มที่มีภาวะน้ำหนักเพิ่มขึ้นตามเกณฑ์อย่างมีนัยสำคัญทางสถิติ (3,240 กรัม กับ 3,080 กรัม, p < 0.001) และดัชนีมวลกายก่อนตั้งครรภ์ ในกลุ่มที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์สูงกว่าในกลุ่มที่มีภาวะน้ำหนักเพิ่มขึ้นตามเกณฑ์อย่างมีนัยสำคัญทางสถิติ (25.1 กิโลกรัมต่อตารางเมตร กับ 22.0 กิโลกรัมต่อตารางเมตร, p < 0.001)*

สรุป: *อัตราภาวะทารกแรกคลอดน้ำหนักเกินพบสูงขึ้นในสตรีตั้งครรภ์ที่มีภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์ โดยมีปัจจัยเสี่ยง ได้แก่ สตรีตั้งครรภ์แรก และภาวะอ้วนหรือมีดัชนีมวลกายก่อนตั้งครรภ์มาก ดังนั้นจึงควรเน้นย้ำถึงความสำคัญของการให้คำแนะนำด้านโภชนาการแก่สตรีตั้งแต่ก่อนตั้งครรภ์รวมไปถึงน้ำหนักตัวที่ควรเพิ่มขึ้นขณะตั้งครรภ์*

คำสำคัญ: *น้ำหนักตัวที่เพิ่มขึ้นขณะตั้งครรภ์, ภาวะน้ำหนักตัวเพิ่มขึ้นเกินเกณฑ์ขณะตั้งครรภ์, ทารกแรกคลอดน้ำหนักเกิน, น้ำหนักหญิงตั้งครรภ์, น้ำหนักทารกแรกเกิด*

Introduction

Neonatal large for gestational age (LGA) is defined as a newborn whose birth weight is at or above the 90th percentile for gestational age at birth[1]. Although most LGA newborns are constitutionally large without any adverse consequences, the rate of maternal and neonatal morbidity is higher in LGA pregnancies[1, 2]. Specifically, risks of postpartum hemorrhage (PPH), shoulder dystocia, and neonatal hypoglycemia linearly increased as the birthweight percentile increased[3]. Later in life, LGA had higher risks of obesity and metabolic syndrome compared with individuals born appropriate for gestational age (AGA)[4]. Consequentially, prenatal diagnosis of LGA fetuses will benefit in perinatal management such as planning delivery and the early identification of pregnant women at risk for having LGA newborns may help in terms of prevention such as modifying risk factors. Although intrauterine growth is influenced by various factors include genetics, race and ethnicity, advanced maternal age, multiparity, maternal obesity, diabetes and postterm gestation, excessive weight gain (EWG) is one of not many factors that can be antenatally controlled[1, 2]. In 2009, the Institute of Medicine (IOM) recommended the appropriate gestational weight gain stratified by pre-pregnancy body mass index (BMI) based on data from Western countries[5, 6]. However, the optimal gestational weight gain may differ in Asians who have smaller body sizes[7]. Therefore, the impact of EWG defined by our local data on fetal growth may be changed. This study aimed to compare the rate of LGA newborns between pregnant women with EWG and appropriate weight gain (AWG) which was classified by local recommendations. The rate of LGA newborns in pregnant women with poor weight gain (PWG) was also analyzed as a secondary outcome.

Materials and Methods

A retrospective cohort study was conducted on pregnant women who delivered singleton newborns between July 2020 and December 2021 at Maharaj Nakorn Chiang Mai Hospital. The maternal and neonatal data were retrieved from the maternal-fetal medicine database and electronic medical records. The exclusion criteria were pregnant women who had incomplete data in medical records, preterm delivery, and pregnant women who had hypertensive disorder. The remaining pregnant women were classified into three groups – 1. PWG, 2. AWG, and 3. EWG by the level of their gestational weight gain calculated by body weight on the date of delivery minus pre-pregnancy body weight in kilograms (kg). The ranges of gestational weight gain in each pre-pregnancy BMI group were 10-18 kg for underweight (BMI < 18.5 kg/m^2), 8-16 kg for normal weight (BMI 18.5-24.9 kg/m^2), 6-14 kg for overweight (BMI 25-29.9 kg/m^2) and 4-8 kg for obesity (BMI > 30 kg/m^2) according to a previous study in Thais[7]. Women who had gestational weight gain that was below, within, and above the optimal ranges were classified as PWG, AWG, and EWG, respectively. Newborns of the participants were classified into three groups – 1. small for gestational age (SGA), 2. AGA, and 3. LGA by their birth weight in grams (g). According to the World Health Organization (WHO) growth standards, newborns who had body weight that was less than the 10th percentile for gestational age (GA), between the 10th and 90th percentile for GA, and more than the 90th percentile for GA were classified as SGA, AGA, and LGA, respectively[8]. Rates of LGA newborns were compared between EWG and AWG groups as well as other data including neonatal birth weight, gender of newborn, GA at delivery, route of delivery, pre-pregnancy BMI, total gestational weight gain, and maternal and neonatal complications. The sample size for a study comparing proportions between two independent groups with discrete data and outcomes measured as proportions can be calculated using the following values: $Z\alpha/2 = 1.96$ for a 5% type I error (two-tailed test), $Z\beta = 0.842$ for 80% power, P1 = 18.5% for LGA in the study group[9], and P2 = 10% in the control group. The average of P1 and P2 (assuming equal group sizes) gave a required sample size of 264 participants per group. To account for a 20% data

loss, 53 additional participants were included, resulting in 317 participants per group. With at least 634 participants in the study, enrollment was retrospectively collected based on the timing of the study period, meaning the actual number of participants may exceed the calculated sample size.

Data was analyzed by using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. All continuous data was not normally distributed as analyzed by the Kolmogorov-Smirnov test. In a comparison of continuous data between AWG and EWG groups, the Mann-Whitney U test was used as appropriate, whereas the chi-square test or Fisher's exact test was used for proportion data. Multivariate logistic regression analysis was used to predict the associated variables of EWG. A p value of less than 0.05 was considered statistically significant.

Results

A total of 1,343 pregnant women with singletons who delivered at Maharaj Nakorn Chiang Mai Hospital from July 2020 to December 2021 were included in the study (Fig. 1). Pregnant women who delivered before 37 weeks of gestation (7.5%) with hypertensive disorders in pregnancy (4.6%) were excluded as well as pregnant women with incomplete data in medical records (0.3%). Of the remaining 1,182 participants, pregnant women with PWG, AWG, and EWG were found in 197 (16.7%), 708 (59.9%), and 277 (23.4%) cases, respectively. The prevalence of SGA, AGA, and LGA newborns was 261 (22.1%), 884 (74.8%), and 37 (3.1%), respectively.

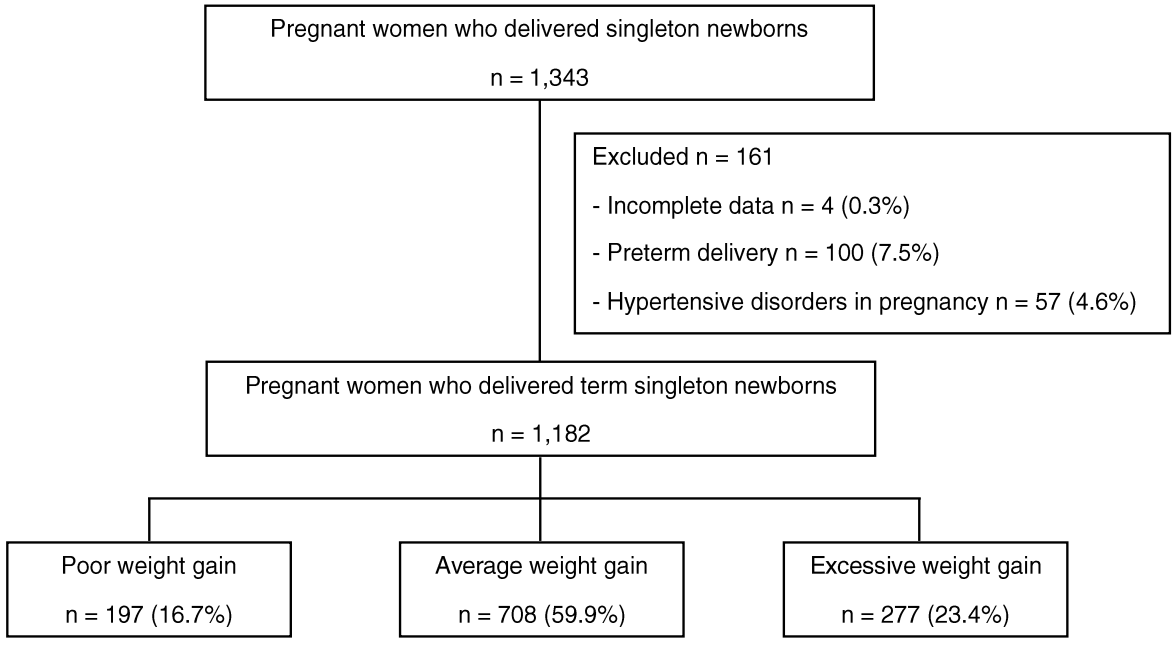

Fig. 1. Flow Diagram of the Study.

Compared with pregnant women in the AWG group, pregnant women in the EWG group had a significantly higher proportion of nullipara, higher pre-pregnancy BMI, and delivered at a later gestational age (Table 1). All continuous data was not normally distributed as analyzed by the Kolmogorov-Smirnov test therefore medians (Q1, Q3) are presented in the table. The prevalence of obesity

was higher in the EWG group than in the AWG group (15.5% and 4.4%, respectively). However, the prevalence of gestational diabetes mellitus (GDM), pre-gestational diabetes mellitus (DM), and insulin treatment during pregnancy were not significantly different between the two groups. The average neonatal birth weight (NBW) was statistically significantly higher in the EWG group than in the AWG group (3,240 gm vs 3,080 gm, p < 0.001). The incidence of LGA newborns was twofold higher in the EWG group than in the AWG group (5.8% vs 2.8%, p = 0.026). Pregnant women with EWG had a higher rate of cesarean delivery, PPH, neonatal respiratory complications, and neonatal intensive care unit (NICU) admission compared to pregnant women with AWG.

Table 1. Baseline characteristics of term pregnant women participants in study.

Characteristics	AWG Group n = 708	EWG Group n = 277	p value
Maternal age (years)	33 (29, 36)	32 (29, 34)	0.095
Nulliparity	385 (54.4%)	170 (61.4%)	0.047
Body mass index (kg/m^2)	22.0 (20.0, 25.4)	25.1 (22.0, 30.4)	< 0.001
Total weight gain (kg)	11.0 (9.0, 13.0)	17.2 (13.0, 19.5)	< 0.001
Maternal and obstetrics complications	65 (100)	51 (92.70)	0.042
Obesity	31 (4.4%)	43 (15.5%)	< 0.001
Gestational diabetes mellitus (GDM)	173 (24.4%)	54 (19.5%)	0.098
Gestational age at diagnosis GDM (weeks)	25 (16, 27)	25 (15, 28)	0.782
Pregestational DM	7 (1.0%)	6 (2.2%)	0.145
Insulin treatment during pregnancy	40 (5.6%)	11 (4.0%)	0.285
Postpartum hemorrhage	13 (1.8%)	13 (4.7%)	0.012
Gestational age at delivery (weeks)	39 (38, 39)	39 (38, 40)	0.001
Route of delivery			
Normal delivery	477 (67.4%)	170 (61.4%)	0.074
Vaginal breech delivery, VE, FE	44 (6.2%)	13 (4.7%)	0.358
Cesarean delivery	187 (26.4%)	94 (33.9%)	0.019
Gender			0.335
Male	382 (54.0%)	140 (50.5%)	
Female	326 (46.0%)	137 (49.5%)	
Neonatal birth weight, grams	3,080 (2,870, 3,388)	3,240 (2,995, 3,500)	< 0.001
Large for gestational age	20 (2.8%)	16 (5.8%)	0.026
Newborn complications			
None	673 (95.1%)	242 (87.5%)	< 0.001
Respiratory complications	15 (2.1%)	18 (6.5%)	0.001
Birth asphyxia	2 (0.3%)	2 (0.7%)	0.315*
Birth injuries	5 (0.7%)	5 (1.8%)	0.155
NICU admission	32 (4.5%)	24 (8.7%)	0.012

Values are presented as n (%) or median (Q1, Q3).

AWG: average weight gain, EWG: excessive weight gain, FE: forceps extraction, NICU: neonatal intensive care unit, VE: vacuum extraction

* Fisher's exact test

The average NBW was gradually increased from the PWG group to the EWG group (Table 2, Fig. 2). The prevalence of LGA was lowest in the PWG group and highest in the EWG group (0.5% and 5.8%, respectively). Conversely, the prevalence of SGA was highest in the PWG group and lowest in the EWG group (31.5% and 14.8%, respectively).

Table 2. Average neonatal birth weight (NBW) and the proportion of small for gestational age (SGA), average for gestational age (AGA), and large for gestational age (LGA) newborns in pregnant women with poor weight gain (PWG), average weight gain (AWG) and excessive weight gain (EWG) groups.

Total n = 1,182	**PWG Group n = 197 (16.7%)**	**AWG Group n = 708 (59.9%)**	**EWG Group n = 277 (23.4%)**	**p value**
NBW (grams)	2,960 (2,735, 3,210)	3,080 (2,870, 3,388)	3,240 (2,995, 3,500)	< 0.001*
SGA n = 261 (22.1%)	62 (31.5%)	158 (23.3%)	41 (14.8%)	< 0.001
AGA n = 884 (74.8%)	134 (68.0%)	530 (74.9%)	220 (79.4%)	0.027
LGA n = 37 (3.1%)	1 (0.5%)	20 (2.8%)	16 (5.8%)	0.001

Values are presented as n (%) or median (Q1, Q3).

*Kruskal Wallis Test

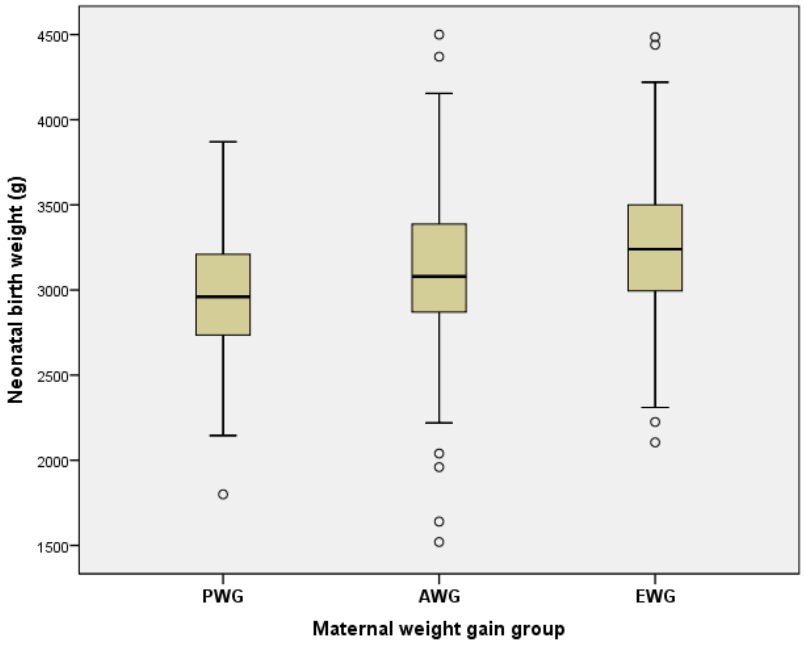

Fig. 2. Boxplots of neonatal birth weight in pregnant women with poor weight gain (PWG), average weight gain (AWG), and excessive weight gain (EWG) groups.

Table 3 shows the relative risk (RR) of EWG in pregnant women analyzed by multivariable logistic regression. Obesity (RR 1.22, 95% CI 1.134, 1.364) and nulliparity (RR 1.45, 95% CI 1.080, 1.944) were the significant independent risk factors for EWG during pregnancy. The other variables such as pregestational DM, GDM, male newborn, and late-term delivery were not found to be significant risk factors.

Table 3. Risk factors of excessive weight gain (EWG) in pregnant women by logistic regression analysis.

Risk factors	Relative Risk	95% Confidence Interval	p value
Gestational diabetes mellitus	1.28	0.882, 1.866	0.193
Pre-gestational diabetes mellitus	0.23	0.049, 1.046	0.057
Obesity (BMI > 30 kg/m^2)	1.22	1.134, 1.364	< 0.001
Nulliparity	1.45	1.080, 1.944	0.014
Male gender	1.18	0.885, 1.568	0.262
Gestational age > 41 weeks	0.89	0.451, 1.735	0.720

Discussion

The 2009 IOM recommends a gestational weight gain of 12.5 - 18.0 kg for underweight women, 11.5 - 16.0 kg for normal-weight women, 7.0 - 11.5 kg for overweight women, and 5.0-9.0 kg for obese women[5]. Our study used Thais' reference ranges that have wider boundaries of the optimal gestational weight gain than the IOM's reference ranges in all pre-pregnancy weight groups[7]. As a result of this wide-ranging guidance, allowed more pregnant women to achieve gestational weight gain within the recommended range. In a 2017 systematic review of more than one million pregnant women, 47% of participants had EWG above the IOM target and 23% had PWG below the IOM target[9]. Compared with our study, only 23.4% of participants had weight gain above the upper limit of Thai's reference ranges, 16.7% had weight gain below the lower limit of Thai's reference ranges and almost 60% had weight gain within the normal limits. As shown in Table 1, obstetrics and newborn complications in the AWG group did not seem to be any different from the general population even though these pregnant women might be in the inappropriate weight gain group according to the IOM's guidelines. This finding helps us support the validity of using Thai's gestational weight gain reference ranges in our practice.

In large systematic review and meta-analysis studies, pregnancy with excessive gestational weight gain has been associated with a higher risk of having LGA newborns 1.4 - 2.5 times compared with normal gestational weight gain and the absolute risk difference was 4%[9-11]. In our study, the incidence of LGA newborns was 3% different and approximately two-fold higher in the EWG group than in the AWG group (5.8% and 2.8%), compatible with and confirming the evidence from previous studies. Despite small changes, the 5% difference or 200-gm increase in neonatal birth weight (3,240 gm in the EWG group and 3,080 gm in the AWG group) was statistically significant and may be meaningful in some pregnant women with specific conditions. The prevalence of LGA newborns in our study was quite low of 3.1% rather than around 10% as in theory. Nevertheless, the review study in Asia found the prevalence of LGA ranged from 4.3% to 22.1%, showing a large variation in prevalence between countries[12]. Moreover, the variation of fetal and

neonatal growth charts used as the reference ranges to define SGA, AGA, and LGA might be one of the reasons.

There have been numerous previous reports about the association between excessive gestational weight gain, GDM, and LGA newborns[13-16]. On the other hand, there have been some reports of non-association similar to our study which did not find any difference in the prevalence of GDM among the EWG and AWG group[17]. However, this controversial issue did not aim to be investigated in our study because of the limitation of the retrospective nature of the study which could not control the treatment intervention in GDM cases. By a multivariable logistic regression analysis, obesity and nulliparity were significant independent risk factors for EWG but the other variables such as male newborn and late-term delivery were not found to be significant risk factors. Maternal pre-pregnancy BMI was also significantly higher in the EWG group than in the AWG group, emphasizing the importance of behavioral counseling intervention to prevent excessive gestational weight gain in this specific population[18]. For the nulliparity variable, the previous study showed the relationship between primiparity and decreased birth weight in contrast to gestational weight gain and increased birth weight[19]. However, the small sample size in our study was a limitation in interpreting this association.

The higher rate of cesarean delivery, PPH, neonatal respiratory complications, and NICU admission in the EWG group compared with the AWG group was found in our study. These findings implied the possibility of complications caused by one or more of three important risk factors – the large mother (overweight and obese), gaining too much weight during pregnancy, and the large fetus. The association between these factors and adverse maternal and neonatal outcomes was established[3, 20, 21]. Therefore, these risks need to be identified and modified during the pre-conceptional and prenatal period. Individual nutrition counseling or group-based educative intervention have been demonstrated to help improve maternal behavior, control dietary caloric intake, and prevent excessive weight gain during pregnancy[22-24].

Although there were some limitations mentioned above, the strength of this study was the definition of gestational weight gain by the local reference ranges which is more compatible with the Asian population. To minimize confounding factors, pregnancies with hypertensive disorder and pregnant women with inadequate weight gain were not included in the comparison between the EWG and AWG groups. Importantly, research findings about EWG in pregnant women which is a common issue in our routine can be applied to improve maternal and child health in real clinical practice.

Conclusion

EWG was associated with a higher rate of LGA in newborns and was likely to occur in women with higher pre-pregnancy BMI and nulliparity. Rates of cesarean delivery, PPH, neonatal respiratory complications, and NICU admission were increased in pregnant women with EWG. EWG should be identified early using the definition by the local reference ranges which are more compatible with the Asian population. Pre-conceptional counseling and pregnancy education on nutrition and weight gain should be implemented and emphasized in routine clinical practice.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 44-52.

OBSTETRICS

Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Levels in the Neonatal Cord Blood and the Serum of Parturients Who Received Coronavirus Vaccine during Pregnancy at Venerable Thawisak Jutindharo Hospital

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ABSTRACT

Objectives: To evaluate the spike antibody (Ab) level in the neonatal umbilical cord blood and serum of mothers vaccinated against coronavirus disease 2019 (COVID-19) during pregnancy and the association between the duration from the last vaccine dose to delivery and the spike Ab level.

Materials and Methods: This study included 75 pregnant women who were vaccinated against COVID-19 (Sinovac, Sinopharm, Astrazeneca, Pfizer, Moderna). Maternal serum and cord blood samples at delivery were collected and analyzed. Then, the association between the duration from the last vaccine dose to delivery and the spike Ab level was analyzed.

Results: Among the participants, 66 (88.0%) and 9 (12.0%) women received two and three COVID-19 vaccine doses, respectively. Spike Ab was detected in the maternal serum and umbilical cords. The median maternal spike Ab level was 2,134.0 (501–5,044) U/mL, and the median umbilical cord spike Ab level was 2,573.0 (791–8,258) U/mL. The duration from the last vaccine dose to delivery was significantly correlated with spike Ab levels in the umbilical cord. Pregnant women who received their last vaccine dose during the third trimester of pregnancy had a higher spike Ab level in the maternal serum and neonatal umbilical cords than those vaccinated in the first and second trimester of pregnancy.

Conclusion: COVID-19 vaccination during pregnancy can transfer antibody to newborn. The shorter duration of last dose of vaccination to delivery, the higher cord blood antibody.

Keywords: antibodies, cord blood, COVID-19 vaccine, maternal immunity, neonatal immunity, pregnancy.

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Received: 22 February 2024, **Revised:** 27 May 2024, **Accepted:** 12 November 2024

ระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 ในเลือดจากสายสะดือของทารกและมารดาที่ได้รับวัคซีนป้องกันโรคโควิดขณะตั้งครรภ์ที่มาคลอดที่โรงพยาบาลหลวงพ่อทวีศักดิ์ ชุตินฺธโร อุทิศ

ลดากานต์ เลิศวรรณวิทย์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 ในเลือดจากสายสะดือของทารกและหญิงตั้งครรภ์ที่ได้รับวัคซีนป้องกันโรคโควิด 19 ขณะตั้งครรภ์และเพื่อศึกษาความสัมพันธ์ระหว่างเวลาที่ได้รับวัคซีนเข็มสุดท้ายจนถึงคลอดกับระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 ในเลือดจากสายสะดือของทารก*

วัสดุและวิธีการ: *การวิจัยนี้เป็นการศึกษาเชิงสังเกตแบบภาคตัดขวางในหญิงตั้งครรภ์ทั้งหมด 75 ราย ที่ได้รับการฉีดวัคซีนป้องกันโรคโควิด 19 (Sinovac, Sinopharm, Astrazeneca, Pfizer, Moderna) อย่างน้อย 2 เข็มขณะตั้งครรภ์ ฝากครรภ์และคลอดที่โรงพยาบาลหลวงพ่อทวีศักดิ์ ชุตินฺธโร อุทิศ ในช่วงเดือนพฤษภาคม 2565 ถึง ตุลาคม 2565 ได้รับการตรวจระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 (spike Ab) และตรวจจากเลือดสายสะดือของทารกขณะคลอด วิเคราะห์หาความสัมพันธ์ระหว่างเวลาที่ได้รับวัคซีนครั้งสุดท้ายก่อนคลอดและระดับภูมิคุ้มกันต่อเชื้อไวรัส ซาร์ส-โควี-2 ในสายสะดือทารก*

ผลการศึกษา: *หญิงตั้งครรภ์ จำนวน 75 ราย ส่วนใหญ่เป็นคนไทย 49 ราย (ร้อยละ 65.3) ได้รับวัคซีนป้องกันโรคโควิด 19 สองโดส จำนวน 66 ราย (ร้อยละ 88.0) และได้รับวัคซีนสามโดส จำนวน 9 ราย (ร้อยละ 12.0) ตรวจพบภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 (Spike Ab) ในเลือดมารดาและสายสะดือทารกทุกราย ค่ามัธยฐานของระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 (Spike Ab) ในมารดา เท่ากับ 2,134.0 U/ml (501-5,044) และสายสะดือทารก เท่ากับ 2,573.0 U/ml (791-8,258) ระยะเวลาที่ได้รับวัคซีนเข็มสุดท้ายก่อนคลอดสัมพันธ์กับระดับภูมิคุ้มกันในสายสะดือทารกอย่างมีนัยสำคัญ ($p = 0.001$) หญิงตั้งครรภ์ที่ได้รับวัคซีนเข็มสุดท้ายในไตรมาสที่สามมีระดับภูมิคุ้มกันต่อเชื้อไวรัสซาร์ส-โควี-2 ในเลือดและ สายสะดือทารกสูงกว่า คนที่ได้รับวัคซีนในช่วงไตรมาสที่หนึ่งและไตรมาสที่สอง*

สรุป: *การฉีดวัคซีนป้องกันโควิด 19 ในหญิงตั้งครรภ์สามารถส่งผ่านภูมิคุ้มกันให้กับทารกในครรภ์ได้ ระยะเวลาจากเข็มสุดท้ายจนถึงคลอดยิ่งสั้น ระดับภูมิคุ้มกันในสายสะดือทารกยิ่งสูง*

คำสำคัญ: *ภูมิคุ้มกัน, เลือดจากสายสะดือทารก, วัคซีนโควิด 19, ภูมิคุ้มกันมารดา, ภูมิคุ้มกันทารก, การตั้งครรภ์*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease of the respiratory system that can cause severe pneumonia and even death. The COVID-19 pandemic has become a serious public health issue[1]. Physiologic changes of respiratory and immunity system increase the risk and severity of infection[2]. Pregnant women, particularly those admitted to the intensive care units and those receiving extracorporeal membrane oxygenation, are at higher risk of mortality than nonpregnant women[3]. Furthermore, COVID-19 is associated with an increased risk of obstetric complications, such as miscarriage, postpartum hemorrhage, and underweight babies[4].

At present, vaccination has been implemented to prevent infection or reduce the severity of COVID-19. At approximately 2–4 weeks after the second COVID-19 vaccine dose, the body can develop sufficient immunity to prevent the disease. Available COVID-19 vaccines[5-7], the efficacy and safety of the COVID-19 vaccines in pregnant women and neonate are reported. Current studies have shown that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine is safe and effective in pregnant women, and it provides the same level of immunity compare with the general population[8].

In Thailand, from April 1, 2021, to November 24, 2021, there were 2,053,129 cases of infections in all age groups and 20,450 cumulative deaths. Further, 59 cumulative child deaths were recorded, with a mortality rate of 0.019%. Mortality is more common in the group aged under 1 year (unvaccinated age group) and the group aged 12–18 years than in the group aged 1–6 and 6–12 years. Children who died had preexisting underlying diseases[9].

Previous study has shown that maternal IgG antibodies respond to vaccinations. Influenza and pertussis vaccination in pregnant women can prevent the infection in newborns. If there are no maternal IgG antibodies, these infections can cause illness and death in newborn.10-12 In 2018, Healy et al[13] reported the association between diphtheria, tetanus, and pertussis (Tdap) vaccination in the third trimester of pregnancy and cord blood immunity. It was found that the group that received the booster vaccine have higher immunity to whooping cough in the umbilical cord blood than in the unvaccinated group (47.3 vs 12.9 IU/mL, $p < 0.001$). Vaccination during the early third trimester (27–30 weeks) was associated with the highest level of pertussis antibody in newborns[14].

The current study aimed to assess the level of immunity against SARS-CoV-2 in the neonatal umbilical cord blood and serum of mothers who received the COVID-19 vaccine during pregnancy. In addition, the association between the duration from the last vaccine dose to delivery and the level of immunity against the SARS-CoV-2 in the neonatal umbilical cord blood was investigated.

Materials and Methods

This cross-sectional study was conducted in pregnant women who were vaccinated against COVID-19 during pregnancy at antenatal care clinic and delivered at Venerable Thawisak Jutindharo Hospital between May 2022 and October 2022. It was performed after obtaining ethics certification from the Bangkok Research Ethics Committee (project code: S005H/65). In total, 78 participants were initially enrolled. However, three patients developed COVID-19 infection, and they were eventually excluded from the study. Finally, 75 participants were analyzed. The inclusion criteria were as follows: 1) singleton pregnancy, 2) aged over 18 years, 3) have been vaccinated against COVID-19 at least two doses, 4) can speak and communicate in Thai. A proof of vaccination, or a history of vaccination in the Ministry of Public Health application was confirmed. In Thailand, both of the regular and cross-type of vaccines were used. The normal

formulations include Sinovac + Sinovac, Sinophram + Sinophram, Astrazeneca + Astrazeneca, Pfizer + Pfizer, Moderna + Moderna, with the second dose administered with an appropriate interval from the first dose according to the type of vaccine used. The cross-type of vaccines were as follows: Sinovac + Astrazeneca, Astrazeneca + Pfizer, Sinophram + Astrazeneca, Sinovac + Pfizer, and Sinophram + Pfizer. The third dose was administered ≥ 3 months after the second dose. The exclusion criteria were as follows: 1) pregnant women with COVID-19 or those with a history of the infection before pregnancy, 2) those with a history of close contact with an infected person, 3) those with immunodeficiency diseases such as congenital immunodeficiency, 4) HIV who are receiving immunosuppressive drugs, and 5) those with maternal or fetal crisis. The number of participants was calculated using the following formula: $n = Z\alpha/2^2\ \sigma^2 / d^2$, σ = standard deviation of population = 64*, d = acceptable allowable error = 15, $Z\alpha/2$ = level of confidence at 95% (two-sided) = 1.96. The formula was based on the study conducted by Lior Kashani-Ligumsky et al[15] (mean neonatal antibody titer = 224.7 ± 64.3 U/mL). The required number of participants was 70, and 10% of the sample size was further required. Hence, the total sample size was 78. The participants provided written informed consent. On the day of delivery, the participants were tested for COVID-19 using an antigen test kit or real-time polymerase chain reaction based on a history of COVID-19 infection. Then, 2 mL of blood was collected from all participants, and 2 mL of umbilical cord blood was obtained at birth using sterile technique. The samples were sent to the laboratory room. The spike protein level was analyzed using the Elecsys machine. The anti-SARS-COV-2 S immunoassay uses recombinant protein, S antigen RBD with the double-antigen sandwich principle. The interpretation of the level of immunity against SARS-CoV-2 was presented as units per milliliter. A negative result was defined as an immunity level of < 0.8 U/mL. Moreover, a positive result was defined as an immunity level of ≥ 0.8 U/mL, with a sensitivity of 98.8% (95% confidence interval 98.1%–99.3%) and a specificity of 99.98% (95% confidence interval 99.91%–100%[16]. The Elecsys machine has been checked 3 times/year and calibrated every 1 year by the staff of Roche Diagnostics at Venerable Thawisak Jutindharo Hospital. After evaluating immunity against SARS-CoV-2 virus, the remaining blood specimens were disposed within 7 days, classified as infectious waste, and discarded according to hospital standards. The level of immunity against SARS-CoV-2 virus was informed to the participants by phone at 2 weeks after collection. Participants with a negative result were advised to have booster vaccination according to the national guidelines at that time. Baseline data including age, race, underlying disease, history of vaccination including types of vaccines, gestational age at vaccination, number of doses received, birth details including gestational age, timing of vaccination, birth weight, Apgar score, and the level of immunity against SARS-CoV-2 spike protein in the maternal serum and umbilical cord blood were recorded. These data were analyzed using the Statistical Package for the Social Sciences software version 27 (IBM Inc.). Quantitative data including age, gestational age at COVID-19 vaccination, gestational age at delivery, duration from vaccination to delivery, birth weight, and immunity level against SARS-CoV-2 spike protein in the umbilical cord and maternal serum were evaluated. Data with a normal distribution were expressed as mean and standard deviation and those with non-normal distribution as median and interquartile range. The association between the duration from the last vaccine dose to delivery and the level of immunity against SARS-CoV-2 in the umbilical cord blood was assessed

using the Pearson chi-square test. A p value of < 0.05 was considered statistically significant. In addition, the Kruskal–Wallis test was utilized to evaluate the association between the gestational age during which the last vaccine dose was administered, and the Spearman correlation was assessed to evaluate the level of immunity against the SARS-CoV-2 spike protein in the maternal serum and umbilical cord blood. A p value of < 0.05 was considered statistically significant.

Results

Of 75 participants, 49 (65.3%) were Thai, and 26 (34.7%) were from other ethnicities. Table 1 shows the baseline characteristics of the participants.

Table 1. Baseline characteristics of the participants (n = 75).

Baseline characteristics	n (%)
Age (years)	28.1 (6.9)*
Race	
Thai	49 (65.3)
Others	26 (34.7)
Gravidity	
First	20 (26.7)
Second	33 (44.0)
Third or more	22 (29.3)
Underlying disease	
Diabetes mellitus	11 (14.7)
Hypertension	2 (2.7)
Anemia	2 (2.7)
Gestational age at delivery (weeks)	38.7 (1.2)*
Preterm labor	5 (6.7)
Birth weight (grams)	3088.5 (367.9)*
Apgar score at 1 minute	9#
Apgar score at 5 minutes	10#

* mean (standard deviation), # median

In total, 66 (88%) pregnant women received two doses of the COVID-19 vaccine, and nine (12%) pregnant women had three doses of the vaccine. All maternal serum and umbilical cord samples tested positive for spike Ab. The average duration from the last vaccine dose to delivery was 142.6 ± 68.4 days. Considering the gestational age which the last vaccine dose was administered, 26 (34.7%) participants received the last dose in the first trimester (< 14 weeks), 32 (42.7%) participants received the last dose in the second trimester (< 28 weeks), and 17 (22.6%) had the last dose in the third trimester (≥ 28 weeks) as shown in Table 2.

Table 2. Vaccination data (n = 75).

Vaccination data	n (%)
Number of doses	
2 doses	66 (88.0)
3 doses	9 (12.0)
Type of the first dose	
Sinovac	10 (13.3)
Sinopharm	22 (29.3)
AstraZeneca	28 (37.3)
Pfizer	14 (18.7)
Moderna	1 (1.4)
Type of the second dose	
Sinovac	4 (5.3)
Sinopharm	14 (18.7)
AstraZeneca	31 (41.4)
Pfizer	25 (33.3)
Moderna	1 (1.3)
Type of the third dose	
Sinovac	-
Sinopharm	-
AstraZeneca	-
Pfizer	9 (12.0)
Moderna	-
Duration from the last dose to delivery (days)	142.6 (68.4)*
Gestational age at last dose	
First trimester (< 14 weeks)	26 (34.7)
Second trimester (14 to < 28 weeks)	32 (42.7)
Third trimester (≥ 28 weeks)	17 (22.6)

* mean (standard deviation)

The median immunity levels against SARS-CoV-2 spike protein in the maternal serum was 2,134.0 (501–5,044) U/mL. The median immunity levels against SARS-CoV-2 spike protein in the umbilical cord blood was 2,573.0 (791–8,258) U/mL.

The level of immunity in the umbilical cord blood was strongly positive correlated with the level of immunity in the maternal serum (correlation coefficient 0.9-1.0, $p < 0.001$) (Fig. 1).

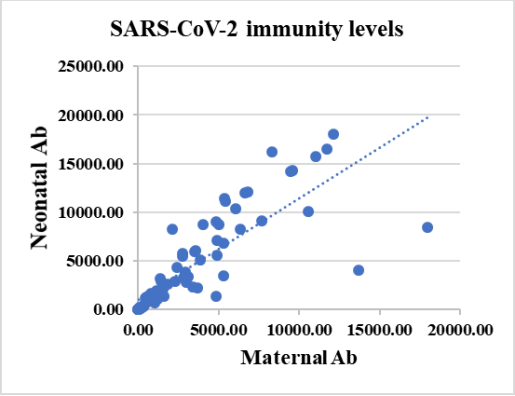

Fig. 1. The correlation between the maternal serum and umbilical cord blood SARS-CoV-2 immunity levels.

The duration from the last vaccination dose to delivery was significantly correlated with immunity levels against the SARS-CoV-2 spike protein in the umbilical cord blood (p = 0.001). There was a significant association between the trimester of pregnancy during which the last vaccine dose was administered and the level of immunity in the maternal serum and umbilical cord blood (p = 0.005 and p = 0.006, respectively). Furthermore, pregnant women who received the vaccine in the third trimester (≥ 28 weeks) had a higher level of immunity against SARS-CoV-2 virus in serum and umbilical cord blood compared with those who received the vaccine in the first trimester (< 14 weeks) and the second trimester (14 to < 28 weeks) (Fig. 2 and 3).

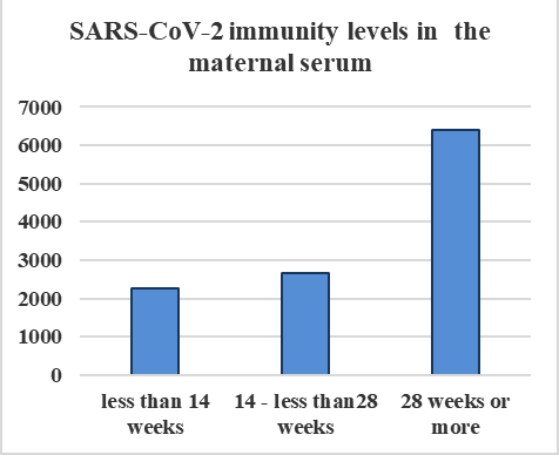

Fig. 2. The relationship between the gestational age at the last dose vaccination and the level of immunity in the maternal serum.

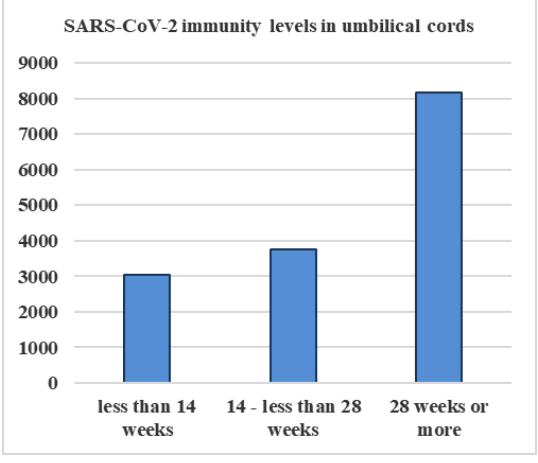

Fig. 3. The relationship between the gestational age at the last dose vaccination and the level of immunity in the umbilical cord blood.

Discussion

This study showed that vaccination against COVID-19 during pregnancy can transfer immunity through the placenta to the fetus. Immunity against

the SARS-CoV-2 virus was observed in the maternal serum and umbilical cord blood. The gestational age at the last vaccine dose was significantly correlated with the level of immunity in the mother and umbilical cord blood ($p = 0.005$ and $p = 0.006$, respectively). Pregnant women who received the last vaccine dose in the third trimester had higher immunity levels against SARS-CoV-2 in the serums and umbilical cords compared with those who received the vaccines during the first and second trimesters. This finding was similar to that of the retrospective study conducted by Wojciech Zdanowski and Tomasz Wasniewski[17], which evaluated the level of immunity in the umbilical cord of infants and the serum of mothers who received the COVID-19 vaccine BNT162b2 mRNA during pregnancy at 29–36 weeks of gestation. In total, 16 samples had an average immunity in all infant umbilical cords (1,026.51 U/mL, standard deviation: 769.25), and the average infant-to-maternal umbilical cord immunity ratio was 1.28 (standard deviation: 0.798), and the relationship between the gestational age of receiving the 1st dose of the vaccine and the ratio of the level of immunity in the umbilical cord and the mother was 0.48, and the relationship between the gestational age of receiving the 2nd dose of the vaccine and the ratio of the level of immunity in the umbilical cord and the mother was 0.39, statistically significant. Infection in newborns born to mothers who received the COVID-19 vaccine may be prevented by passing placental immunity. Moreover, immunity levels are associated with the duration from vaccination to delivery.

Fu et al[18] conducted a systematic review of research on the safety, immunization, and efficacy of COVID-19 vaccines in pregnant and breast-feeding women. Of 23 studies, 8 were used the Pfizer vaccine, 14 about the Pfizer and Moderna vaccines, and 1 about the Astrazeneca vaccine. These studies showed that immunity was found in the blood of pregnant women, umbilical cord blood, and breast milk. The cord blood antibody concentration/maternal serum antibody concentrations differed in each report, with five studies showing that a high IgG antibody concentration in the umbilical cord was associated with the second COVID-19 vaccine dose before birth. Furthermore, there was an association between an increased level of IgG antibodies in the umbilical cord blood and the duration from the first dose of the COVID-19 vaccine to delivery. These results were similar to our study.

Amihai Rottenstreich et al[19] evaluated the level of immunity in infants born to pregnant women vaccinated in the early and late stages of the third trimester. Results showed that vaccination in the early phases of the third trimester might prevent COVID-19 in newborns.

Since this study was conducted during emergency situations in Thailand, several companies have introduced COVID-19 vaccines. The use of several types of vaccines may result in different immunity levels. In this study, the number of pregnant women vaccinated during the third trimester was not sufficient to perform an analysis about the early and late phases of the third trimester. However, immunity levels in maternal serum and cord blood were higher if they received the second COVID-19 vaccine dose in the third trimester of pregnancy.

The current study had several strengths. That is, it was prospective in nature, and the participants who had a history of COVID-19 infection were excluded to ensure that only the level of immunity from vaccination was evaluated. However, it also had several limitations. That is, emergency situations and the country's policy at the time; therefore, the use of different COVID-19 vaccines and formulations might have affected immunity levels.

Conclusion

COVID-19 vaccination during pregnancy can pass immunity to the fetus. The shorter duration of last dose of vaccination to delivery, the higher cord blood antibody.

Acknowledgements

The authors acknowledge the effort of the entire team of the Department of Obstetrics and Gynecology,

Venerable Thawisak Jutindharo Hospital, Thailand for making this work possible.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 53-63.

GYNAECOLOGY

The Impact of Ginger on Preventing Postoperative Ileus after Hysterectomy Under the Enhanced Recovery after Surgery Protocol: A randomized controlled trial

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ABSTRACT

Objectives: To investigate the impact of ginger supplementation on postoperative ileus following hysterectomy under the enhanced recovery after surgery protocol.

Materials and Methods: A randomized controlled trial with investigator blinding was conducted. The control arm followed the enhanced recovery after surgery pathway exclusively, while the intervention arm received ginger supplementation. The outcomes assessed postoperatively were bowel function, tolerability of oral intake, wound complications, and adverse effects of treatment.

Results: One hundred and sixty patients participated, with 80 allocated to each arm. The median duration of the operative procedure was 130 minutes (Interquartile range [IQR], 105 to 165). Within the first 12 hours postoperatively, 41 patients (25.6%) reported the passage of flatus, and 46 patients (28.8%) experienced ileus. All patients resumed a solid diet within 24 hours. When comparing the control arm to the ginger arm, no significant differences emerged with respect to the postoperative ileus time interval (14.7 ± 7.8 vs 13.6 ± 8.4 hours, p = 0.432), time until the first passage of flatus (17.3 ± 8.1 vs 17.1 ± 7.9 hours, p = 0.869), time to start a solid diet (11.7 ± 6.1 vs 11.2 ± 6.6 hours, p = 0.660), and time to well tolerate a solid diet (18.6 [IQR 14.6 to 20.9] vs 17.3 [IQR 6.2 to 20.1] hours, p = 0.596). The length of the hospital stay did not differ significantly. No adverse effects related to ginger or instances of febrile morbidity were observed.

Conclusion: Ginger supplementation did not significantly reduce the incidence of postoperative ileus or the recovery of bowel function following hysterectomy under the enhanced recovery after surgery protocol.

Keywords: bowel function, ginger, hysterectomy, ileus.

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Received: 24 August 2024, **Revised:** 4 November 2024, **Accepted:** 7 November 2024

ผลของการใช้ขิง เพื่อช่วยลดการเกิดภาวะลำไส้ไม่ทำงานภายหลังผ่าตัดมดลูก: การศึกษาควบคุมแบบสุ่ม

ปรียนันท์ พงศ์ศุภนิมิต, เรวิกา ไชยโกมินทร์, พินภัทร ไตรภัทร, วุฒินันท์ อัจฉริยะโพธา, บุญเลิศ วิริยะภาค, สุดารัตน์ กลั่นเพชรพะเนา, ณัฐชนน สถาปนพิทักษ์กิจ, ไอรีน เรืองขจร

บทคัดย่อ

วัตถุประสงค์: *ศึกษาผลของการใช้แคปซูลขิงร่วมกับการส่งเสริมการฟื้นตัวหลังผ่าตัด (enhanced recovery after surgery) ต่อการช่วยลดการเกิดภาวะลำไส้ไม่ทำงาน (postoperative ileus) ภายหลังผ่าตัดมดลูก*

วัสดุและวิธีการ: *การศึกษาควบคุมแบบสุ่ม โดยที่กลุ่มควบคุมได้รับการรักษาตามแบบแผนการส่งเสริมการฟื้นตัวหลังผ่าตัดทางนรีเวช และกลุ่มทดลองได้รับประทานแคปซูลขิงร่วมกับการรักษาตามแบบแผนการส่งเสริมการฟื้นตัวหลังผ่าตัดทางนรีเวช ผู้วิจัยที่ทำการประเมินอาสาสมัครหลังผ่าตัดไม่ทราบว่าอาสาสมัครถูกจัดอยู่กลุ่มใด โดยประเมินการทำงานของลำไส้หลังผ่าตัด การรับประทานอาหารได้ ภาวะแทรกซ้อนของแผลผ่าตัด และผลข้างเคียงที่เกิดจากการรับประทานแคปซูลขิง*

ผลการศึกษา: *อาสาสมัครทั้งหมดจำนวน 160 คน ถูกแบ่งออกเป็น กลุ่มละ 80 คน โดยมีค่ากลางของเวลาทำการผ่าตัดอยู่ที่ 130 นาที เมื่อติดตามภายหลังการผ่าตัด 12 ชั่วโมง มีผู้ป่วยจำนวน 41 คน (ร้อยละ 25.6) สามารถผายลมได้ และ 46 คน (ร้อยละ 28.8) เกิดภาวะลำไส้ไม่ทำงาน เมื่อเปรียบเทียบกลุ่มควบคุมและกลุ่มทดลอง พบว่า ไม่มีความแตกต่างกันในระยะเวลาของการเกิดภาวะลำไส้ไม่ทำงานหลังผ่าตัด (14.7 ± 7.8 vs 13.6 ± 8.4 ชั่วโมง, p = 0.432) ระยะเวลาหลังผ่าตัดจนกระทั่งผายลมครั้งแรก (17.3 ± 8.1 vs 17.1 ± 7.9 ชั่วโมง, p = 0.869) ระยะเวลาหลังผ่าตัดจนกระทั่งเริ่มรับประทานอาหารปกติ (11.7 ± 6.1 vs 11.2 ± 6.6 ชั่วโมง, p = 0.660) และระยะเวลาหลังผ่าตัดจนกระทั่งรับประทานอาหารปกติได้ดี (18.6 [IQR 14.6 to 20.9] vs 17.3 [IQR 6.2 to 20.1] ชั่วโมง, p = 0.596) รวมถึงระยะเวลาในการนอนโรงพยาบาลในอาสาสมัครทั้งสองกลุ่มก็ไม่แตกต่างกัน ไม่พบผลข้างเคียงจากการใช้แคปซูลขิง ไม่พบภาวะไข้หลังผ่าตัด*

***สรุป**: การรับประทานแคปซูลขิง ไม่ช่วยลดการเกิดภาวะลำไส้ไม่ทำงาน และไม่ช่วยให้การทำงานของลำไส้ฟื้นตัวกลับมาได้เร็วขึ้นอย่างมีนัยสำคัญ ภายหลังผ่าตัดมดลูกและให้การดูแลรักษาตามแบบแผนการส่งเสริมการฟื้นตัวหลังผ่าตัดทางนรีเวช*

***คำสำคัญ**: การทำงานของลำไส้, ขิง, ตัดมดลูก, ภาวะลำไส้ไม่ทำงาน*

Introduction

Postoperative ileus (POI) is an acknowledged complication following hysterectomy, with observed rates between 10% and 30% and exceeding 40% in surgeries involving gynecologic cancers[1-4]. Ileus is triggered by peritoneal irritation that activates the sympathetic nervous system. Typically, the condition presents with decreased motility of the bowel smooth muscle and resolves over 2 to 3 days. The small bowel regains function within 6 - 12 hours postoperatively, the stomach within 24 - 48 hours, and the large bowel within 48 - 72 hours[5, 6]. Traditionally, posthysterectomy patient care involved nasogastric intubation until indications of gastrointestinal functions such as hunger, passage of flatus or stool, or bowel sounds were apparent, followed by a gradual reintroduction of oral intake[7]. Currently, the enhanced recovery after surgery (ERAS) pathway following hysterectomy is considered the standard of care[2, 7-9]. These interventions include, but are not limited to, the early initiation of water, juice, tea, and coffee intake; ice sucking; early feeding; metoclopramide; and gum chewing[6, 10-14].

Ginger (Zingiber officinale Roscoe) is an aromatic herb from the Zingiberaceae family. It contains compounds such as 6-gingerol and 6-shogoal that have been shown to inhibit serotonin (5-HT3) receptors, antineurokininergic, digestive and gastrointestinal motility-enhancing properties. Clinical trials have confirmed ginger's effectiveness in reducing nausea, vomiting, and inflammation and treating constipation, bloating, and flatulence[15, 16]. Data on the benefits of ginger following hysterectomy are limited. Most studies have focused on outpatient laparoscopic gynecologic surgeries and cesarean sections, where 1-2 grams of ginger are administered preoperatively. The primary objective of these studies has been to assess its effect on postoperative nausea and vomiting, rather than exploring other potential benefits, such as complications reduction, or enhanced recovery[15, 17]. This study aimed to compare the incidence of POI and provide a qualitative assessment of bowel recovery by evaluating the time required to resume a solid diet between the study groups. Other comparisons related to the recovery of bowel function, postoperative complications, and length of hospital stay.

Materials and Methods

Following authorization from the Siriraj Institutional Review Board (approval number: Si-124/2023) and the Thai Clinical Trial Registration (TCTR no. 20230228001). We carried out a randomized controlled trial with investigator blinding. Recruitment of participants spanned from March to July 2023. Patients scheduled for hysterectomy who did not need oral intake restrictions after surgery were included in the study. Informed consent was obtained from all subjects.

After the surgery, participants who met the inclusion criteria were randomly assigned to one of two study arms using a block randomization method with groups of four. IR generated the allocation sequence before the study without any contact with the participants. The control group followed the ERAS protocol, starting with sips of liquids 3 - 4 hours after

surgery and progressing to a solid diet, as long as there was no vomiting. In addition to the ERAS protocol, the intervention group received a dose of ginger as a 1-g capsule 3 - 4 hours after the operation and another 1 g following each meal, amounting to 9 doses throughout the study duration[16]. NS stored and distributed ginger capsules to the participants. A placebo control was not employed owing to concerns over the potential adverse effects of starch within the placebo capsule on bowel function.

PP blinded to the participants' study arms, evaluated the postoperative outcomes of all participants. We recorded postoperative outcomes, which encompassed bowel functions, tolerance to oral intake, wound complications, and any adverse effects arising from ginger consumption. Surgical complications were monitored until 30 days after the surgery.

Our sample size was based on Schilder et al's study on women undergoing major abdominal gynecologic surgery. In their study, women who started early sipping consumed a regular diet within 1.88 ± 0.14 days, which was significantly faster than the control group[10]. We expected the ginger group to achieve a regular diet intake approximately 1.55 days, or 8 hours (0.33 days) earlier than the controls, with a standard deviation of 0.564 days. Aiming for 90% power, we set the type I error (α) at 0.05 and the type II error (β) at 0.1. Each arm was calculated to require 62 women. After accounting for an attrition rate of 20%, the total sample expanded to 160 women.

Data analyses were performed using SPSS Statistics (version 29; IBM, Armonk, New York, USA). The results were presented as counts and percentages or medians with interquartile ranges (IQRs). The continuous data was compared by student t test or Mann-Whitney U test. The chi-square or Fisher's exact test was applied for categorical variable comparisons. We considered a p value of less than 0.05 as indicative of statistical significance. All analyses were conducted following the intent-to-treat principle.

Our study employed the following specific terms:

- "Well-tolerated solid diet." We defined this as the successful consumption of at least half of a meal comprised of a solid diet without vomiting.
- "Postoperative day" (POD). We delineated POD 0 as the period starting from the end of the surgery and lasting for the subsequent 24 hours; POD 1 as the 24 - 48 hour interval after completion of surgery; POD 2 as 48 - 72 hours following surgery; and POD 3 as 72 - 96 hours after the completion of the surgery.
- "POI." Diagnosis of this condition adhered to Vather's criteria, requiring at least 2 of the following 5 symptoms: (1) nausea with or without vomiting, (2) inability to ingest a regular diet persisting for 24 hours or longer, (3) failure to pass flatus or stool for 24 hours or more, (4) clinically apparent abdominal distention, and (5) radiological confirmation of ileus. The term "prolonged POI" was applied if these symptoms were present from POD 4 onwards[18].
- "POI time interval." This duration was calculated from the conclusion of surgery to the initial passage of flatus or stool, in conjunction with the ability to tolerate a solid diet[18].
- "Febrile morbidity." This condition was categorized as registering a body temperature of 38.3 °C or above on two occasions, separated by a minimum of 6 hours, beginning from POD 1[19].
- "Discharge criteria." The criteria for patient discharge were achieving full ambulation, initiating or tolerating a solid diet, and maintaining pain management with oral analgesics.
- "Length of stay (LOS)." The duration was calculated from the end of the surgery to the point when patients met the discharge criteria.

Results

The Fig. 1. depicts the distribution of 160 participants allocated evenly between the two arms, with 80 individuals per arm. Baseline demographic

and surgical characteristics and a comparison between the two study arms are detailed in Table 1. The median duration of surgery was 130 minutes (IQR 105.0-165.0). By the end of POD 1, POI was identified in one individual within the control arm: the condition resolved by POD 3 following treatment with an osmotic laxative. This 49-year-old patient underwent a total abdominal hysterectomy to remove a myoma uteri, performed under a spinal block. Her operation lasted 140 minutes, with an estimated blood loss of 1,000 mL. The patient had no surgical complications and did not experience an extended hospital stay due to delayed oral intake or nausea. Her LOS was 70.3 hours.

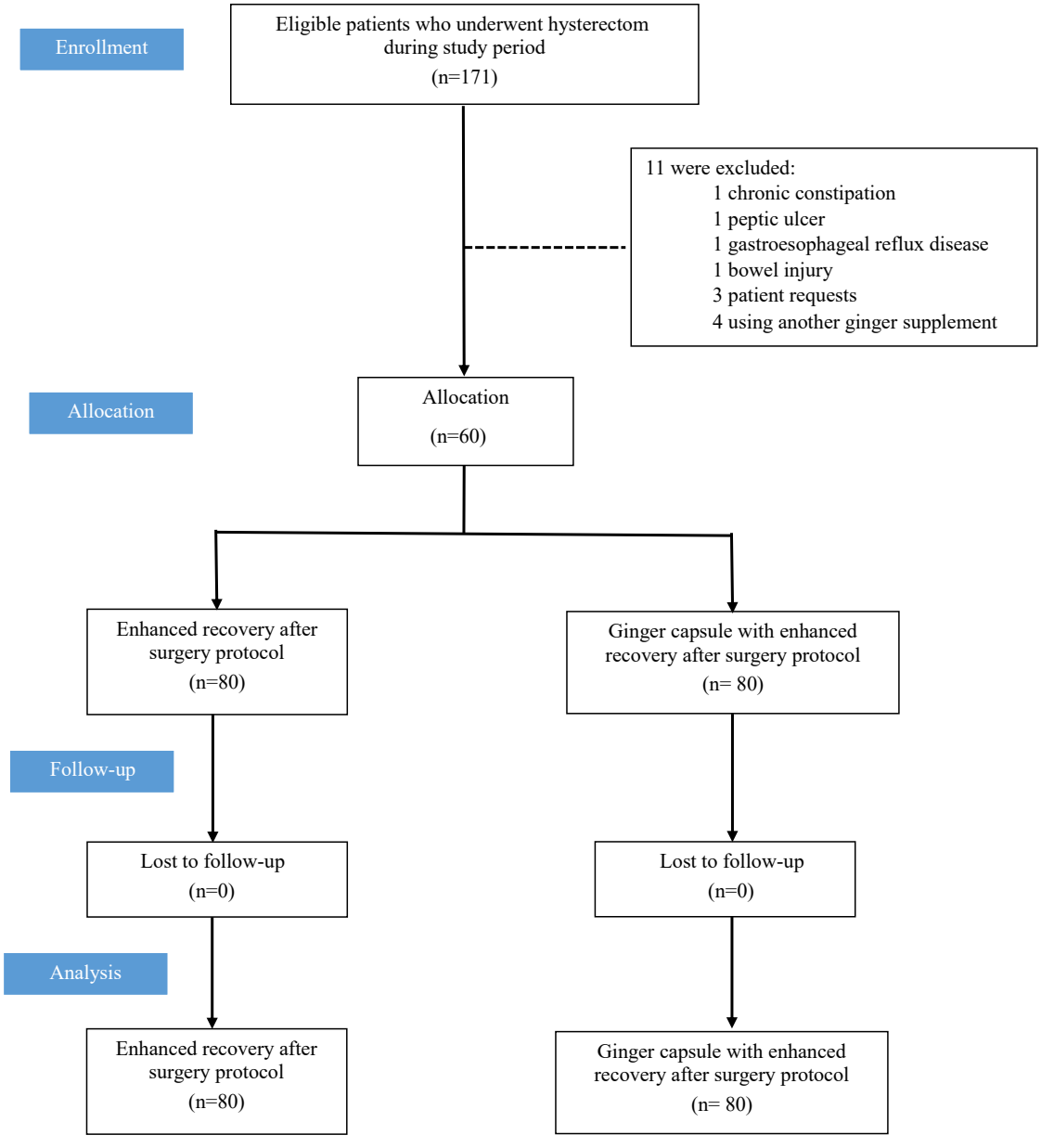

Fig. 1. Flow Diagram of the Study.

Table 1. Comparison of the baseline and surgical characteristics of the two study arms.

Variables	Control group (n = 80)	Ginger group (n = 80)	p value
Age (years)	47.1 ± 8.6	48.7 ± 6.9	0.174
BMI (kg/m^2)	24.9 ± 4.8	25.0 ± 4.5	0.868
Diseases			
Benign	70 (87.5%)	74 (92.5%)	0.292
Malignant	10 (12.5%)	6 (7.5%)	
ASA classification			
I	28 (35.0%)	35 (43.8%)	0.141
II	45 (56.3%)	42 (52.5%)	
III	7 (8.8%)	3 (6.3%)	
IV	0	0	
Diabetes mellitus	9 (11.3%)	1 (1.3%)	0.009
Alcohol, currently using	7 (8.8%)	11 (13.8%)	0.317
Smoking, currently using	1 (1.3%)	2 (2.5%)	1.000
Preoperative hemoglobin (g/dL)	12.2 ± 1.4	12.3 ± 1.4	0.932
Preoperative painkillers within 2 weeks	78 (97.5%)	73 (91.3%)	0.167
Preoperative proton pump inhibitor used	30 (37.5%)	33 (41.3%)	0.627
Preoperative metoclopramide used	21 (26.3%)	19 (23.8%)	0.715
Fasting time (hours)			
From regular diet	23.9 ± 2.7	23.7 ± 1.9	0.684
From sip water	7.9 ± 2.4	7.7 ± 1.9	0.582
Surgical approaches			
Exploratory laparotomy	50 (62.5%)	42 (52.5%)	0.201
Laparoscopy	30 (37.5%)	38 (47.5%)	
Adhesiolysis	24 (30.0%)	25 (31.3%)	0.864
Surgical time (mins)	134.5 ± 46.8	143.1 ± 54.7	0.286
Estimated blood loss (mL)	100 (50-250)	125 (50-250)	0.545
Anesthetic methods			
Spinal block with morphine	36 (45.0%)	27 (33.8%)	
General anesthesia	33 (41.3%)	47 (58.8%)	
Combined	11 (13.8%)	6 (7.5%)	
Had general anesthesia component	44 (55.0%)	52 (65.0%)	0.197
Subtemperature event	14 (17.5%)	10 (12.5%)	0.376
Intravenous fluid positive (mL)	1525.0 (757.5-2150.0)	1495.0 (612.5-2187.5)	0.716
Intraoperative morphine used	35 (43.8%)	45 (56.3%)	0.114
Intraoperative morphine (mg)	5.8 ± 2.7	6.8 ± 2.5	0.118
Intraoperative fentanyl used	66 (82.5%)	68 (85.0%)	0.668
Intraoperative fentanyl (mg)	77.3 ± 26.2	85.1 ± 33.2	0.134
Intraoperative xylocaine used	25 (31.3%)	29 (36.3%)	0.504
Intraoperative ondansetron used	62 (77.5%)	69 (86.3%)	0.151
Intraoperative metoclopramide used	5 (6.3%)	9 (11.3%)	0.263
Postoperative opioids used	17 (21.3%)	13 (16.3%)	0.418
Postoperative antiemetics used	45 (56.5%)	44 (55.1%)	0.932
Postoperative simethicone used	50 (62.5%)	51 (63.7%)	0.870
Routine as physician preference	25	26	
On request	25	25	
Routine postoperative omeprazole	35 (44.3%)	43 (53.8%)	0.234
Postoperative laxative need	20 (25.0%)	19 (23.8%)	0.854
Postoperative coffee drinking	7 (8.8%)	10 (12.5%)	0.442

Values are mean ± SD unless otherwise noted.
ASA: American Society of Anesthesiologists physical status, BMI: body mass index, NG: nasogastric, POD: postoperative day

No significant differences were found between the control and ginger arms (Table 2) regarding the POI time interval, time to first flatus, time to initiate a solid diet, or time to adequately tolerate a solid diet. Within the initial 12 hours following surgery, 41 patients (25.6%) reported passing flatus. A total of 39 patients (24.4%) requested laxatives. All patients resumed a regular diet within 24 hours. While a greater proportion of patients in the ginger group successfully tolerated their initial regular diet compared to the control group (75.0% vs 65.0%, p = 0.168), this difference did not achieve statistical significance. No adverse events associated with ginger intake, febrile morbidity, or surgical site infection were observed.

Table 2. Postoperative outcomes of the participants.

Variables	Control group (n = 80)	Ginger group (n = 80)	p value
Time to first flatus (hours)	17.3 ± 8.0	17.1 ± 7.9	0.869
Vomiting or emesis	39 (48.8%)	36 (45.0%)	0.635
After POD0	11	8	
Vomit	26	19	
Need medications	12	8	
Bloating or distension	36 (45.0%)	35 (43.8%)	0.874
Abdominal discomfort exceeding 24 hours	31 (38.8%)	28 (35.0%)	0.623
Epigastric pain	26 (32.5%)	25 (31.3%)	0.865
POI time interval (hours)	14.7 ± 7.8	13.6 ± 8.4	0.432
Time to flatus	17.3 ± 8.1	17.1 ± 7.9	0.869
Flatus in 12 hours	21 (26.3%)	20 (25.0%)	0.856
Flatus in 24 hours	67 (83.8%)	70 (87.5%)	0.499
Belch detected	50 (62.5%)	58 (72.5%)	0.177
POI occurred	23 (28.8%)	23 (28.8%)	1.000
POI types			
Upper	10	16	
Lower	9	4	
Total	4	3	
POI on POD			
POD0	19	15	
POD1	2	8	
POD2	1	0	
POD3	1	0	
NG intubation for POI treatment	0	0	
Time to first solid diet (hours)	11.7 ± 6.1	11.2 ± 6.6	0.660
Time to well tolerate solid diet (hours)	18.6 (14.6-20.9)	17.3 (6.2-20.1)	0.596
Solid diet within 12 hours	35 (43.8%)	37 (46.3%)	0.751
Well tolerated solid diet on first attempt	40 (50.0%)	44 (55.0%)	0.527
Additional bowel stimulants	20 (25.0%)	19 (23.8%)	0.854
Time to get out of bed (hours)	18.1 ± 3.8	17.5 ± 4.5	0.391
Pain score, maximum level of the day			
POD0	4 (2-6)	3 (1-5)	0.494
POD1	2.5 (1-4)	2 (1-3)	0.866
Ambulation time duration (mins)			
POD1	40 (25-50)	47.5 (25-50)	0.568
POD2	50 (25-50)	45 (25-50)	0.516
POD3	30 (25-50)	27.5 (25-50)	0.256
Foley catheter removal time (hours)	17.2 ± 8.3	16.6 ± 5.9	0.623
Length of hospital stay (hours)	57.3 ± 18.1	53.6 ± 16.6	0.180

Values are mean ± SD unless otherwise noted.
NG: nasogastric, POD: postoperative day, POI: postoperative ileus

Discussion

Our findings indicated that ginger did not demonstrably hasten the restoration of bowel function or accelerate the transition to oral dietary consumption. While a higher proportion of participants in the ginger arm could successfully tolerate their initial regular diet compared to the control group, the difference was not statistically significant. No ginger-related side effects, febrile morbidity, or surgical site infections were observed and also there were no POI cases persisted beyond POD 3. The median times for resuming a regular diet within 24 hours and for Foley catheter removal were consistent with current standard recommendations[2]. Our study served as a contemporary benchmark on the timing for the resumption of bowel function and eating capabilities in the context of the ERAS pathway.

The etiology of POI is multifaceted and not wholly comprehended. It contributes significantly to perioperative morbidity and can lead to delayed postoperative treatment and financial strain—an ongoing challenge in both prevention and management. Various clinical and pharmacological interventions have been tested. They range from acupuncture, preoperative walking, early diet resumption, chewing gum, drinking coffee, dietary fiber, and various treatments such as 5HT4 receptor agonists, milk of magnesia, bisacodyl suppositories, osmotic laxatives, vagal nerve stimulation, peripheral opioid antagonists, antiflatulence drugs, prokinetic agents, and herbal medicines[1, 2, 6, 10, 12, 20-25].

In the Schilder et al's study, women who had major abdominal surgery started a clear liquid diet on POD 1 and progressing to a regular diet after tolerating 500 mL of clear liquids. The early feeding strategy reduced the time interval to solid diet consumption from an average of 2.72 ± 0.14 days to 1.88 ± 0.14 days ($p < 0.001$)[10]. Similarly, Pearl et al reported the early feeding regimen could consume a solid diet sooner (2.3 ± 2.4 days vs 4.2 ± 1.5 days, $p < 0.001$). The regimen also led to earlier detection of bowel sounds (1.8 ± 1.2 days vs 2.3 ± 1.2 days, $p = 0.007$) and resulted in a shorter LOS (4.6 ± 2.1 days vs 5.8 ± 2.7 days, $p = 0.001$)[22]. Additionally, it decreased the LOS from 4.02 ± 0.30 days to 3.12 ± 0.16 days ($p = 0.008$). However, patients in the early feeding group experienced a higher rate of nausea and emesis episodes, significantly[10, 22]. In our study, the time to tolerate a solid diet, time to first flatus, and LOS were shorter compared to two previous studies. This may be due to the inclusion of both exploratory and laparoscopic procedures in our study population.

The use of chewing gum in patients who had exploratory laparotomies for benign gynecologic conditions had a decreased occurrence of postoperative nausea (31.4% vs 50.0%, $p = 0.049$) and a shorter interval to the first flatus (30.8 ± 17.7 vs 42.2 ± 17.1 hours, $p = 0.08$)[21]. In cases of undergoing total laparoscopic hysterectomy, chewing gum significantly reduced the time to first bowel movement, with 27.2 ± 5.8 hours for the nonchewing group and 23.6 ± 4.3 hours for the gum-chewing group ($p = 0.001$). Additionally, it increased the percentage of women with first bowel sounds heard within 5 hours, from 59.0% to 85.9% ($p = 0.001$)[23]. Ginger supplementation in the current study also resulted in a shorter time to tolerate a solid diet, time to first flatus, and LOS. This may be attributed to the use of the ERAS protocol in our study. Additionally, ginger acts through receptor-based mechanisms, while chewing gum improves gastrointestinal function via reflex mechanisms.

The effects of coffee on gut function recovery were assessed in women undergoing total abdominal hysterectomy and retroperitoneal lymph node dissection for gynecologic cancer, showing significant improvements in postoperative recovery. It resulted in shorter times to flatus (29.7 ± 4.9 vs 41.6 ±1 0.9 hours, $p < 0.001$), audible bowel movement (35.6 ± 5.4 vs 47.5 ± 11.7 hours, $p < 0.001$), and defecation (42.0 ± 6.8 vs 59.8 ± 14.6 hours, $p < 0.001$). Additionally, coffee drinkers tolerated a solid diet sooner (3.5 ± 1.2 vs 4.8 ± 1.6 hours, $p < 0.001$), had a shorter LOS (6.1 ± 1.1 vs 7.4 ± 2.9 days, $p = 0.003$), and experienced fewer ileus symptoms (13.8% vs 51.8%, $p < 0.001$)[23]. Additionally, there was no

significant difference in the enhancement of bowel function recovery between the 50 mg and 100 mg doses of caffeine[13]. Coffee consumption was linked to a lower incidence of POI, possibly due to its rapid effects on colonic motor activity within four minutes. However, the time to tolerate a solid diet, time to first flatus, and LOS were longer than the current study, likely because of the implementation of the ERAS protocol.

Fanning et al examined patients who underwent radical hysterectomy and utilized 30 mL of milk of magnesia bid on POD 1 and a bisacodyl rectal suppository on POD 2, combined with early feeding after the passage of flatus. The researchers cited a POI rate of 0.8%, a median time to flatus of 3 (range 2–3) days, a time to bowel movement of 3 (range 2–5) days, and an LOS of 4 (range 3–7) days[1, 26]. A similar study, a protocol incorporating a clear liquid diet and an oral sodium phosphate solution on POD 1 was used to enhance bowel functions. The median time to flatus was 2.6 (range 2–6) days, and the median time to stool was 2.8 (range 2–7) days, with an LOS of 3.5 (range 3–7) days[25]. Another study involving an oral laxative combination (magnesium oxide and disodium phosphate) found that the laxative group experienced a significant reduction in defecation time, with the median time decreasing from 69 hours to 45 hours ($p < 0.001$). No significant changes were noted in pain scores, nausea, or LOS[24]. These studies noted a longer time to first flatus, and LOS than the current study, but also had the small proportion of POI incidence.

In a randomized, placebo-controlled trial involving postcesarean women, participants consumed 1 g of ginger in capsule form three times daily from POD 1 to POD 4. On POD 4, the group receiving ginger had significantly milder abdominal distention, displayed a more significant improvement in eating ability, achieved earlier bowel movements, and exhibited no notable adverse effects[16, 20]. Conversely, administering 1.5 gm of ginger orally 1 hour before laparoscopic procedures for benign gynecologic conditions did not produce a significant decrease in nausea or vomiting at 2 or 6 hours postoperatively compared with placebo (10% vs 20%, $p = 0.278$, and 23.3% vs 46.7%, $p = 0.058$, respectively)[17].

In the present study, ginger supplementation failed to significantly accelerate bowel function restoration or enhance oral intake readiness more effectively than the standard ERAS protocol. Three hypotheses can rationalize the results. First, hysterectomy surgery may entail more extensive manipulation or irrigation of the small and large intestines than cesarean section procedures. Second, human pharmacokinetic studies indicate that oral absorption of ginger exceeding 1 gm leads to detectable active metabolites in the bloodstream within 30 minutes, reaching maximal levels between 45 and 120 minutes and complete elimination by the 4-hour mark[27]. Last, a systematic review found that a daily dosage of 1–2 grams effectively alleviate nausea or vomiting induced by pregnancy, chemotherapy, and postoperative conditions, as well as improves gastroesophageal function. For significant gastrointestinal motility effects, a ginger dosage as high as 4 gm/day—the amount employed for ailments such as irritable bowel syndrome or gastroenteritis—was reported to be effective[11, 28]. Therefore, future investigations targeting POI following hysterectomy should consider the preoperative administration of ginger 1 hour before surgery and a total daily intake of 4 gm.

This randomized study's strengths included the exclusive focus on hysterectomy patients and the precise definition of outcomes such as POI, well-tolerated diet, and POD, with postoperative complications tracked up to 30 days. The main limitations included the allowance for other antiflatulent or laxative agents among participants and the absence of defecation data for all subjects (attributable to early discharge in laparoscopic cases).

Future research should investigate the potential benefits of ginger in cases of exploratory laparotomy, particularly with increased dosing and preoperative administration, to maximize perioperative efficacy.

Conclusion

Ginger supplementation did not significantly reduce the incidence of POI or the recovery of bowel function following hysterectomy under the enhanced recovery after surgery protocol.

Acknowledgements

The authors gratefully acknowledge Mr Suthipol Udompunturak for assistance with the statistical analyses, and Miss Sarocha Boonkate an administrative officer overseeing funding management. The authors are also indebted to Mr David Park for editing this paper in English.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 64-76.

OBSTETRICS

Willingness to Receive a COVID-19 Vaccine among Pregnant Thai Women during the COVID-19 Pandemic

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ABSTRACT

Objectives: To determine the level of acceptance of COVID-19 vaccine among pregnant women residing in Thailand during the COVID-19 pandemic and assess sociodemographic, medical and informational factors influencing their acceptance.

Materials and Methods: Online and paper-based questionnaires were distributed to pregnant women attending the prenatal care clinic in hospitals located in different regions of Thailand between July and October 2021. Sociodemographic characteristics, perception of risks and knowledge on COVID-19 were collected. Participants were given information on composition, safety and effectiveness, but not the commercial name and manufacturers, of the three currently available COVID-19 vaccines and were asked about their vaccine acceptance. Logistic regression analysis was used to determine factors associated with vaccine acceptance.

Results: A total of 138 women completed the questionnaire. Fifty-nine percent of participants were willing to receive the Thai FDA-approved COVID-19 vaccines. mRNA vaccines (BNT162b2) had the highest acceptance (59.4%) followed by an inactivated (CoronaVac) whole virion vaccine (29.7%) and ChAdOx1-S adenoviral-vectored vaccine (17.4%). The major reason for hesitancy was safety of the mother and fetus. The degree of reliability of COVID-19 vaccine information sources was highest in personal obstetricians and lowest in state media. Pregnant women with adequate knowledge on COVID-19 had higher vaccine acceptance rates. There was no difference in the occupation, education, income, or presence of comorbidities between vaccine acceptance and vaccine hesitancy groups.

Conclusion: Safety was the major reason for vaccine hesitancy, but adequate knowledge on COVID-19 can promote vaccine acceptance in Thailand.

Keywords: acceptance, hesitancy, COVID-19, pregnant women, vaccine.

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Received: 30 August 2023, **Revised:** 5 September 2024, **Accepted:** 10 September 2024

การยอมรับวัคซีนป้องกันโรคติดเชื้อไวรัสโคโรนา 2019 ในหญิงตั้งครรภ์ที่อาศัยอยู่ในประเทศไทยช่วงที่มีการระบาดของโรคติดเชื้อไวรัสโคโรนา 2019

พลอยกวิญญ์ ชัยเกียรติ, ฟ้าใส เชี่ยวบางยาง, บุณยวีร์ วงศ์วิเศษสุข, นิชานันท์ เนตตกุล, พริบพราวดาว สุวรรณสิงห์, สุรสิทธิ์ ชัยทองวงศ์วัฒนา, สตีเฟน เคอร์, ณศมน วรรรลภากร

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาอัตราและปัจจัยที่สัมพันธ์กับการยอมรับวัคซีนป้องกันโรคติดเชื้อไวรัสโคโรนา 2019 ในหญิงตั้งครรภ์ที่อาศัยอยู่ในประเทศไทยช่วงที่มีการระบาดของโรคติดเชื้อไวรัสโคโรนา 2019*

วัสดุและวิธีการ*: เป็นการศึกษาที่จุดเวลาใดเวลาหนึ่ง โดยเก็บข้อมูลจากหญิงตั้งครรภ์ที่มารับบริการที่คลินิกฝากครรภ์ ณ โรงพยาบาลต่างๆ ในประเทศไทยระหว่างเดือนกรกฎาคม ถึง ตุลาคม พ.ศ. 2564 ผ่านแบบสอบถามรูปแบบออนไลน์หรือกระดาษ ข้อมูลที่เก็บ ได้แก่ ข้อมูลพื้นฐาน เช่น อายุ อายุครรภ์ รายได้ และ การศึกษา และข้อมูลเกี่ยวกับโรคติดเชื้อไวรัสโคโรนา 2019 เช่นความเสี่ยงของการติดเชื้อ และความรู้เกี่ยวกับตัวโรคและวัคซีนป้องกัน นอกจากนี้แบบสอบถามได้ให้ข้อมูลเกี่ยวกับ ส่วนประกอบ ความปลอดภัย และประสิทธิภาพของวัคซีนป้องกันโรคติดเชื้อไวรัสโคโรนา 2019 จำนวนสามชนิด ที่ใช้ในประเทศไทย ณ เวลานั้น โดยไม่เปิดเผยชื่อและผู้ผลิตและถามผู้เข้าร่วมวิจัย ว่ายอมรับที่จะฉีด วัคซีนชนิดนั้นๆ หรือไม่ และเหตุผลหากไม่แน่ใจหรือไม่ยอมรับ ข้อมูลเหล่านี้ ถูกนำมาวิเคราะห์ เพื่อหาอัตราและปัจจัยที่ส่งผลต่อการยอมรับวัคซีนป้องกันโรคติดเชื้อไวรัสโคโรนา 2019*

ผลการศึกษา*: จากผู้เข้าร่วมงานวิจัยทั้งหมด 138 ราย ร้อยละ 59.4 เลือกที่จะรับวัคซีนชนิด mRNA ตามด้วยวัคซีนชนิดเชื้อตายซึ่งมีอัตรายอมรับเท่ากับร้อยละ 29.7 และวัคซีนชนิดมีไวรัสเป็นพาหะร้อยละ 17.4 สาเหตุหลักที่ทำให้เกิดความลังเลใจในการรับวัคซีนคือความกังวลด้านความปลอดภัยต่อมารดาและทารกในครรภ์ แหล่งข้อมูลที่หญิงตั้งครรภ์เชื่อถือมากที่สุดในการตัดสินใจที่จะรับวัคซีนคือสูติแพทย์ผู้ดูแลครรภ์ ส่วนแหล่งข้อมูลที่เชื่อถือน้อยที่สุดคือข้อมูลจากภาครัฐ การที่หญิงตั้งครรภ์มีความรู้พื้นฐานเกี่ยวกับตัวโรคและวัคซีนอย่างเพียงพอ สัมพันธ์กับอัตราการยอมรับวัคซีนที่สูงขึ้น*

***สรุป**: ความกังวลด้านความปลอดภัยของวัคซีนป้องกันโรคติดเชื้อไวรัสโคโรนา 2019 เป็นสาเหตุหลักที่ทำให้เกิดความลังเลใจในการรับวัคซีนในหญิงตั้งครรภ์ที่อาศัยอยู่ในประเทศไทยช่วงที่มีการระบาดของโรคติดเชื้อไวรัสโคโรนา 2019 และการให้ความรู้ที่ถูกต้องอาจช่วยเพิ่มอัตราการยอมรับวัคซีนได้*

***คำสำคัญ**: การยอมรับวัคซีน, หญิงตั้งครรภ์, โรคติดเชื้อไวรัสโคโรนา 2019*

Introduction

Pregnant women infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are at increased risk for severe morbidity and mortality compared with non-pregnant women of the same age[1,2]. SARS-CoV-2 infection in pregnancy is associated with a higher risk of premature delivery, preeclampsia, stillbirth, intensive care unit admission, invasive ventilation, extracorporeal membrane oxygenation, and death[3-6]. In the early phases of coronavirus disease starting in 2019 (COVID-19) vaccine development, vaccines were tested on healthy adult individuals, not pregnant women or children. Inclusion of pregnant women in the novel COVID-19 vaccine trials would have allowed evaluation of safety and efficacy of vaccines that might reduce maternal morbidity from COVID-19 and improve pregnancy and birth outcomes. However, clinical trials of new vaccines often excluded pregnant individuals for several reasons, including ethical concerns about fetal exposure, actual and perceived regulatory barriers, and liability concerns[7].

During the early COVID-19 pandemic and initial vaccine roll-out, there was limited information on the safety and efficacy of the COVID-19 vaccine in pregnant mothers. This created confusion and concern among pregnant women on whether to receive a vaccine with limited available safety, immunogenicity and efficacy data. A previous survey from 16 countries showed that, given a 90% COVID-19 vaccine efficacy, only 52% of pregnant women indicated they would receive the vaccine. Predictors of vaccine acceptance included confidence in vaccine safety or effectiveness, worrying about COVID-19, personal beliefs, trust of public health guidelines and attitudes towards routine vaccination[8]. A metanalysis conducted in May 2021 reported that the pooled intention rate for receipt of COVID-19 vaccine among pregnant women was 47% (95% confidence interval (CI) 38 – 57%) with substantial variations according to country of residence[9]. The authors also found that uptake of other vaccines (influenza and/or Tetanus-diphtheria and acellular pertussis; TdaP) during pregnancy was associated with higher rates of intention to receive the COVID-19 vaccine (odds ratio (OR) 3.03 (95%CI 1.37 – 6,73)[9]. A Turkish study reported an even lower acceptance rate of 37% among pregnant women[10].

In February 2021, Thailand began importing inactivated COVID-19 vaccine (CoronaVac,®) developed by Sinovac Life Sciences, Beijing, China. This was followed in March 2021 by Oxford/AstraZeneca's Chimpanzee adenovirus Oxford 1 (ChAdOx1)-vectored vaccine, containing spike glycoprotein of SARS-CoV-2 (ChAdOx1-S), which was initially imported from Korea, and later produced locally by Siam Bioscience (Nonthaburi, Thailand). The third available vaccine imported to Thailand in August 2021 was Pfizer/BioNTech's BNT162b2 mRNA vaccine. Although Thailand initially managed to contain the spread of COVID-19, in late May 2021, the readily transmissible delta variant SARS-CoV-2 first found in India was detected domestically. The delta variant spread rapidly in Bangkok and other

provinces, causing a substantial rise in numbers of COVID-19 cases and deaths[11]. In August 2021, there were reports of fatal cases of COVID-19 in Thai pregnant women, all of whom were unvaccinated or incompletely vaccinated[12].

With the development of multiple effective vaccines, reducing the global morbidity and mortality of COVID-19 will depend on equitable vaccine distribution and acceptance of COVID-19 vaccination. Since pregnant mothers are often key decision-makers for whether or not they accept vaccinations, it is important to measure the level of vaccine acceptance in this group and understand the reasons contributing to their decision making. Such data can help individual countries prepare for COVID-19 vaccination rollout. In this study, we aimed to determine the level of acceptance of the three COVID-19 vaccines available at the time of the study (CoronaVac, ChAdOx1-S, and BNT162b2) among pregnant women residing in Thailand, and assess sociodemographic, medical and informational factors influencing their acceptance.

Materials and Methods

Study design and data collection

We conducted an anonymous, online and paper-based survey among pregnant women attending antenatal care visits in hospitals or clinics in Thailand between July and October 2021. The online-based survey was distributed by obstetricians throughout Thailand. We assessed COVID-19 vaccine acceptance level, baseline risk and knowledge about COVID-19, trust in COVID-19 information from different media, and attitudes towards vaccine acceptance and hesitancy. This study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 530/64, COA No. 940/2021). This study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided consent before filling out the questionnaire. Inclusion criteria were Thai pregnant women aged 18 years or older who could read and write in Thai and provide consent to participate in the study. Exclusion criteria included pregnant women who were unable to provide informed consent or who had a history of or were currently infected with COVID-19.

Sample size and sampling

The sample size was calculated using the formula for a confidence interval around a population proportion[13]. We assumed the COVID-19 vaccine acceptance rate would be approximately 50% among Thai pregnant women attending antenatal clinics. This assumption was based on an acceptance rate of 52% in a previous study[8], and because a rate of 50% gives the maximum sample size for any given level of precision. Enrolling 96 women would allow this rate to be with a precision of approximately ±10%. In this study, we employed convenience sampling, a non-probability sampling technique where participants were selected based on their availability and willingness to participate.

Questionnaire

The questionnaire (Supplementary file 1) used in this study was newly developed for pregnant women in response to the emergence of COVID-19, as there were no existing validated questionnaires at the time the study was conducted. The questions were derived from previously published literature by the same authors[14,15] and relevant literature[8]. Additionally, while the pilot study to pre-test comprehension of the questionnaire and improve the clarity and language included only five pregnant women, thematic sufficiency was achieved, and no further comments or modifications were necessary after the fourth. The pilot test improved the questionnaire by clarifying what “high risk” and “low risk” of contracting COVID-19 mean and by adding a timeframe to assess the risks, which we defined as 3 months. “High risk” refers to situations such as close contact with foreign tourists, being in crowded places, having contact with many people, being front-line healthcare workers, those who must use public transportation, or those unable to work from home. Additionally, we included questions about how many household members were at “high

risk" of contracting COVID-19, as these could influence pregnant women in their decision to get vaccinated.

The questionnaire was structured into four sections covering participants' sociodemographic characteristics, perceived COVID-19 risks and attitudes towards other vaccines, fundamental knowledge about COVID-19 and COVID-19 vaccine, reliability of sources for participants who want to research more about COVID-19 vaccines and acceptance of COVID-19 vaccine. In the fundamental knowledge section, the authors included four Yes/ No/ Unsure questions. Participants who correctly answered at least 3 of 4 questions were classified as having adequate knowledge. Furthermore, there were three specific scenarios on vaccine safety and efficacy provided. Participants were given information on composition, and current safety and effectiveness, of the three available vaccines in Thailand. This information was taken from the available literature[16,17] and a review of COVID-19 vaccines' efficacies and adverse reactions by the CEB COVID-19 evidence team from Ramathibodi Hospital[18]. The commercial name and manufacturers were withheld to decrease the bias caused by the overwhelming discussion about these vaccinations in the Thai media. Participants were given the option to indicate whether they were willing, unsure, or unwilling to receive the vaccines. Those who answered "willing" were defined as individuals who expressed a willingness to receive the vaccine. Those who were unwilling or unsure were also asked to provide reasons for their hesitancy. Vaccine hesitancy is defined as individuals who respond with "unsure" or "unwilling" regarding the vaccine, indicating a delay or refusal to accept the vaccine despite its availability[19]. Conversely, vaccine acceptance refers to the intention to receive the vaccine, as indicated by those who express willingness in our questionnaire. It is important to note that vaccine hesitancy reflects individuals' decision-making process or thought process about the vaccine, irrespective of whether they have actually received it at that time. The first vaccine was an inactivated COVID-19 vaccine; Coronavac (Sinovac Biotech Ltd., People's Republic of China), or Vaccine S[20]. The second vaccine was an adenovirus vector vaccine; ChAdOx1-S/nCoV-19 (University of Oxford - AstraZeneca Plc., United Kingdom), or Vaccine A[16], and the third vaccine was BNT162b2 mRNA vaccine from BioNTech/Pfizer or Vaccine P[17].

Statistical analysis

Statistical analysis was conducted using Stata 17 (Statacorp, College Station, TX, USA). Continuous data were described by 'willingness to vaccinate' group according to data distribution as mean standard deviation (SD) or median interquartile range (IQR), and formal comparisons made by a t-test or Wilcoxon rank sum test as appropriate. Categorical data were described as frequency (percent), and formal comparisons between groups made using Fisher's exact test. No continuous data was transformed. We used logistic regression to assess associations between individual variables and willingness to receive a COVID-19 vaccine, for variables with p values ≤ 0.15 in two group comparisons. In these models, education was dichotomized as university education or lower. The final multivariable model was selected by the combination of variables which minimized the Akaike information criterion (AIC), and model adequacy was tested using the Hosmer and Lemeshow goodness of fit test. A p value of < 0.05 was considered statistically significant.

Results

Participants' sociodemographic characteristics and vaccine acceptance rates

A total of 146 responses were recorded, with 103 from the online questionnaire and 43 from the paper-based version. However, 8 participants from the online survey declined to participate. Thus, a total of 138 responses from 138 pregnant women were included in this study. Acceptance rate of COVID-19 vaccination during pregnancy was 59.4% (95%CI; 50.7 - 67.7). There were no significant demographic differences between the vaccine

acceptance and vaccine hesitancy groups. Most of the pregnant women who responded to the questionnaire were in their third trimester (61.6%), with no difference in the mean age between the vaccine acceptance and vaccine hesitancy groups (32.4 vs 31.5 years, p = 0.26). Among the 138 respondents, 53.6% had a bachelor's degree, 25.4% had a master's degree or higher, 16% graduated from high school or held an associate's diploma, and 4.4% had a middle school diploma or lower. Most of the enrolled participants (84%) had no co-morbidities. However, 8.0 % (n = 11) had diabetes mellitus, 0.7% had hypertension (n = 1), 0.7% had heart disease (n = 1), and the rest (n = 8) had other comorbidities Human Immunodeficiency Virus (HIV) positive, obesity, lung disease). There was no difference in the occupation, education, income, or presence of comorbidities between vaccine acceptance and vaccine hesitancy groups. Participants' characteristics and demographic data stratified by vaccine acceptance are shown in Table 1.

Table 1. Respondents' socio-demographic and vaccine knowledge adequacy by vaccine acceptance group.

Characteristics	Acceptance (n = 82)	Hesitancy (n = 56)	p value
Mean (SD) age (years)	32.4 (4.1)	31.5 (4.5)	0.26
Median (IQR) gestational age (weeks)	29 (21 – 34)	28 (23 – 36)	0.32
Gestational age (categories)			
0 - 12 wk, n (%)	9 (11.0%)	3 (5.3%)	0.26
13 - 27 wk, n (%)	22 (26.8%)	17 (30.3%)	
28 - 40 wk, n (%)	51 (62.2%)	34 (60.7%)	
Unknown, n (%)	0 (0.0%)	2 (3.6%)	
Occupation, n (%)			0.47
Civil Servant	10 (12.2%)	5 (8.9%)	
Merchant	3 (3.7%)	4 (7.1%)	
State Enterprise	4 (4.9%)	0 (0.0%)	
Freelance	8 (9.8%)	7 (12.5%)	
Office worker	32 (39.0%)	29 (51.8%)	
Personal business	13 (15.8%)	5 (8.9%)	
Unemployed/retired	5 (6.1%)	2 (3.6%)	
Others	7 (8.5%)	4 (7.1%)	
Education, n (%)			0.07
Elementary school	1 (1.2%)	1 (1.8%)	
Middle school	0 (0.0%)	4 (7.1%)	
High school	9 (11.0%)	7 (12.5%)	
Diploma	2 (2.4%)	4 (7.1%)	
Bachelor	46 (56.1%)	28 (50.0%)	
Masters	24 (29.3%)	11 (19.6%)	
No answer	0 (0.0%)	1 (1.8%)	
Income (n)			0.83
≤ 20,000 baht*	13	10	
20,001 - 50,000 baht	23	18	
> 50,000 baht	15	11	
Don't want to answer	31	17	

Table 1. Respondents' socio-demographic and vaccine knowledge adequacy by vaccine acceptance group. (Cont.)

Characteristics	Acceptance (n = 82)	Hesitancy (n = 56)	p value
Significant comorbidities, n (%)			0.41
None	66 (80.5%)	50 (89.3%)	
Diabetes mellitus	8 (9.8%)	3 (5.4%)	
Heart disease	1 (1.2%)	0 (0.0%)	
Hypertension	0 (0.0%)	1 (1.8%)	
Others	6 (7.3%)	2 (3.6%)	
Don't want to answer	1 (1.2%)	0 (0%)	
Perceived risk of COVID-19 infection, n (%)			0.41
Low	62 (75.6%)	43 (76.8%)	
High	17 (20.7%)	13 (23.2%)	
Don't want to answer	3 (3.7%)	0 (0.0%)	
Number of household members, n (%)			0.34
1-2	25 (30.5%)	19 (33.9%)	
3	15 (18.3%)	7 (12.5%)	
4 or more	42 (51.2%)	29 (51.8%)	
Don't want to answer	0 (0.0%)	1 (1.8%)	
Number of household members (Including participants) at high risk of COVID-19 infection, n (%)			0.21
0	4 (4.9%)	2 (3.6%)	
1	38 (46.3%)	28 (50.0%)	
2	25 (30.5%)	18 (32.1%)	
3 or more	14 (17.1%)	4 (7.1%)	
Don't want to answer	1 (1.2%)	4 (7.1%)	
Friends, family/ or colleagues have contracted COVID-19, n (%)			0.93
Yes	25 (30.5%)	16 (28.6%)	
No	56 (68.3%)	39 (69.6%)	
Don't want to answer	1 (1.2%)	1 (1.8%)	
Friends, family, or colleagues have received a COVID-19 vaccine, n (%)			0.15
Yes	69 (84.1%)	40 (71.4%)	
No	12 (14.6%)	15 (26.8%)	
Don't want to answer	1 (1.2%)	1 (1.8%)	
Respondent has received other vaccines during pregnancy, n (%)			0.68
Yes	65 (79.3%)	42 (75.0%)	
No	17 (20.7%)	14 (25.0%)	
Adequate vaccine knowledge, n (%)			0.001
Yes	72 (87.8%)	35 (62.5%)	
No	10 (12.2%)	21 (37.5%)	

* 1 USD = approximately 33.5 baht. The minimum daily wage is 313-336 baht per day.

Perception of COVID-19 risks, attitudes towards other vaccines and fundamental knowledge on COVID-19 and COVID-19 vaccine.

A total of 105/138 (76.1%) participants reported themselves as having "low risk" of contracting COVID-19. There was no difference in the percentages of perceived low risk between vaccine acceptance and vaccine hesitancy groups (75.6% vs 76.8%, p = 0.41). However, 17.1% of the vaccine acceptance group had 3 or more family members at high risk of contracting COVID-19, compared to only 7.1% in the vaccine hesitancy group, although this did not reach statistical significance. There was no difference in the percentages of participants who had a family member, friends, work colleagues or relatives who contracted COVID-19 between vaccine acceptance and vaccine hesitancy groups (30.5% vs 28.6%, p = 0.93). Most participants (79.0%) reported that their family, friends, or colleagues have been vaccinated with COVID-19 vaccine, and most had (77.5%) had received other vaccines during pregnancy. There was no difference in the percentages of participants who had previously received other vaccines, such as influenza, pertussis, and tetanus, between the vaccine acceptance and vaccine hesitancy groups.

Regarding the fundamental knowledge on COVID-19 and COVID-19 vaccines, 77.5% of the participants (n = 107) had adequate knowledge. Factors associated with COVID-19 acceptance during pregnancy at p < 0.15 are shown in Table 2. In the multivariable analysis, after adjustment for university education or lower, the only significant association with willingness to vaccinate was adequate knowledge on COVID-19 and vaccine (adjusted OR 4.03, 95%CI 1.69 - 9.61, p = 0.002). While university education was not a significant association, the adjusted odds ratio for this variable was 1.91, and the 95%CI were predominantly consistent with higher willingness to be vaccinated. The Hosmer and Lemeshow goodness of fit p value was 0.25, indicating adequate model fit.

Table 2. Univariable and multivariable logistic regression model of factors associated with willingness to receive the Thai FDA approved COVID-19 vaccine.

Characteristics	Univariable		Multivariable	
	OR (95%CI)	p value	aOR (95%CI)	p value
University education vs high school or lower	2.39 (1.03 - 5.57)	0.04	1.91 (0.78 - 4.7)	0.16
Know someone vaccinated against COVID-19	1.91 (0.85 - 4.31)	0.12		
Vaccine knowledge adequate (vs inadequate)	4.3 (1.8 - 10.2)	0.001	4.03 (1.69 - 9.61)	0.002

FDA: Food and Drug Administration, COVID-19: Coronavirus Disease 2019, OR: odds ratio, aOR: adjusted odds ratio.

Acceptance of each type of COVID-19 vaccine and reasons for vaccine hesitancy

Based on information on the composition, safety, and effectiveness of each vaccine type, the mRNA vaccine (BNT162b2) had the highest acceptance (59.4%) followed by the inactivated (CoronaVac) whole virion vaccine (29.7%) and the ChAdOx1-S adenoviral-vectored vaccine (17.4%). Fig. 1 illustrates the distribution of reasons pregnant women may have concerns or hesitations about receiving different types of COVID-19 vaccines. In Fig. 1, the most common reason for hesitancy across all vaccine types was concern that both the pregnant woman and the fetus would experience adverse effects from the COVID-19 vaccine. Other major reasons included "prefer receiving a safer vaccine",

"prefer receiving a more effective vaccine", "want to wait for more evidence to confirm safety of the vaccine in pregnant women" and "does not trust information from governmental organization".

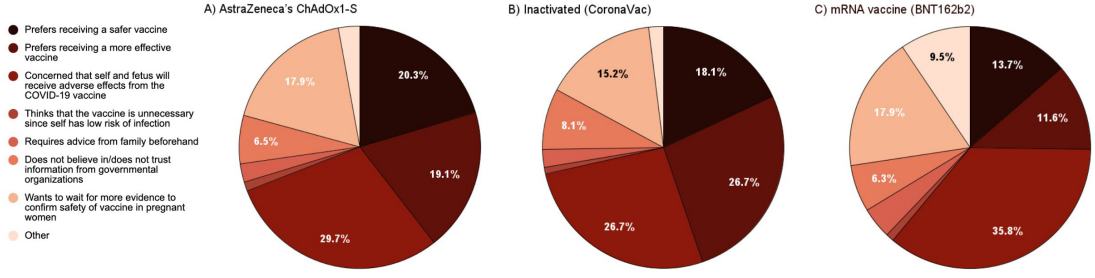

Fig. 1. The major reasons for unwillingness or hesitancy to receive A) an adenoviral-vectored vaccine B) an inactivated vaccine C) an mRNA vaccine.

Reliability of sources if participants want to research more about COVID-19 vaccine.

Pregnant women were asked to rank the sources that they trust the most when seeking information about COVID-19 vaccines. Fig. 2 illustrates the perceived reliability of various information sources, as rated by the respondents. The sources provided in the questionnaire included the government's "THAI ROO SOO COVID" facebook and twitter, the government's coronavirus disease management center on the television, guidance from the Ministry of Public Health, Thailand, acquaintance and family members, personal obstetricians, and online platforms such as social media and websites. The rankings ranged from "not reliable at all" (1) to "strongly reliable" (4). According to this study, the degree of reliability of COVID-19 vaccine information sources was rated highest for personal obstetricians, with 65.2% of respondents ranking this source as "strongly reliable." Conversely, the government's coronavirus disease management center on television was rated the lowest in reliability.

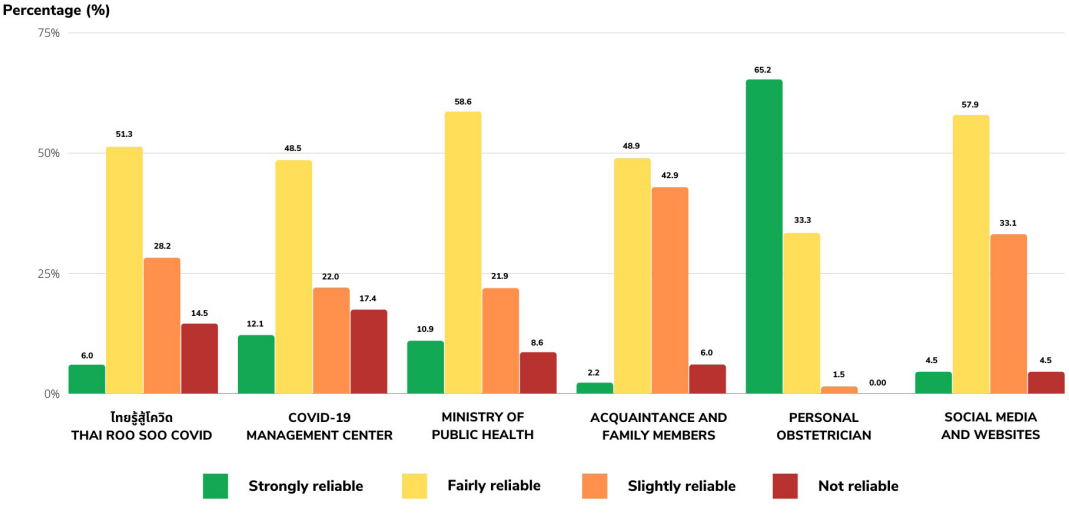

Fig. 2. Reliability of COVID-19 information sources ranging from strongly reliable (green), fairly reliable (yellow), slightly reliable (orange) and non-reliable (red).

Discussion

Vaccine confidence is increasingly recognized as an important element in determining the success of vaccine uptake in regions where vaccine accessibility is optimal. As of August 2021 when this study was conducted, Thailand has secured inactivated vaccine, adenoviral-vectored vaccine and mRNA vaccines. In this study, we found 59% of pregnant women who participated were willing to receive any of the Thai-FDA approved COVID-19 vaccines. The vaccine acceptance rate in this cohort was higher than other previous studies, which reported an acceptance rate between 37-53%[8-10, 21-22]. We hypothesized that geographic variation may influence COVID-19 vaccination acceptance rates among pregnant women. For instance, a survey by Skjefte et al[8] in 16 countries found higher acceptance levels in the tropical regions such as Philippines, India, and Latin America, and lower levels in the temperate region such as US, Australia, and Russia. Nirunrungruang et al conducted a prospective study in rural Chiang Mai, Thailand, one year after our study, reporting even lower vaccine acceptance rates (17%) among pregnant women[23]. This contrasts with the higher acceptance rates found in our study, which involved participants mainly from Bangkok, the country's urban center. This suggests that cultural and regional factors significantly impact vaccine acceptance. Another consideration is the potential selection bias in our study. As this study used convenience sampling, participants likely to get vaccinated may have been more willing to respond to the questionnaire, while those who hesitated may not have responded, potentially leading to an overestimation of acceptance rates. Therefore, the actual COVID-19 vaccine acceptance rate among pregnant women in Thailand may be low, highlighting the need for an intervention strategy to promote acceptance.

As per vaccine type, the mRNA vaccine had the highest acceptance rate, probably due to the high efficacy in preventing mild and moderate symptoms of COVID-19 (95% for mRNA vaccine as compared to 84% for inactivated and 79% for adenoviral-vectored vaccines). Besides, at the time the questionnaire was administered, the mRNA vaccine was the only vaccine that had been used in pregnant women with preliminary data showing that there were no reports of higher adverse events following vaccination. The most common reason for vaccine hesitancy was safety of maternal and the fetus, which was similar to the previous studies on COVID-19 vaccine acceptance during pregnancy in the US and Turkey, and Chiang Mai, Thailand[10,21,23]. Other common reasons for vaccine hesitancy found in this study were "prefer receiving more effective vaccine", "wait for more evidence to confirm safety of the vaccine in pregnant women" and "does not trust information from governmental organization". These findings aligned with the scoping review of global COVID-19 vaccine hesitancy by Casubhoy et al[24], who reviewed 44 articles on attitudes toward COVID-19 vaccination among pregnant women and found that the primary reason for vaccine hesitancy was a lack of confidence in vaccine safety and fear of unknown side effects. Other factors influencing hesitancy according to Casubhoy et al included lack of access to reliable information about the vaccine and mistrust of the vaccine and medical professionals[24].

This study also found that adequate knowledge on COVID-19 and vaccine was the only factor significantly associated with willingness to vaccinate, after adjusting for education level. A study on influenza vaccine acceptance in Thai pregnant women also found that women in the influenza vaccine acceptance group scored higher in knowledge on influenza and vaccine (83.2% vs 73.9%) than those in the hesitancy group[13]. Similarly, a study on pertussis vaccine acceptance in Thai pregnant women also found that knowing the disease could improve the intention to receive pertussis vaccine during pregnancy[14].

Educational levels have been shown to be associated with increased rates of COVID-19 vaccine acceptance in a study of the Thai elderly population.[25] Although education level was not significant in our multivariable model, including it as an explanatory variable resulted in a better model fit,

and the adjusted odds ratio and 95%CI for university education were consistent with an increased willingness to vaccinate. A systematic review and meta-analysis in the United States found that pregnant women with college or higher education were significantly more likely to accept the COVID-19 vaccine, with an odds ratio of 3.25 (95% CI 2.53 - 4.17[26]. Additionally, predictors of COVID-19 vaccine acceptance have been shown to be related to attitudes towards routine vaccine[8]. A metanalysis showed that uptake of other vaccines (influenza and/or Tetanus-diphtheria and acellular pertussis; TdaP) during pregnancy was associated with higher rate of intent to receive the COVID-19 vaccine[9, 26, 27]. Women with higher levels of education may be more likely to make more informed and evidence-based decisions about their health.

In terms of resources for Thai pregnant women to consult with regarding the COVID-19 and vaccine, personal obstetricians ranked first with highest reliability. These findings were consistent with the previous studies on pertussis and influenza vaccines in Thailand, Hong Kong and United Kingdom which reported that recommendation of vaccine by healthcare providers greatly improved the acceptance rate[13-14, 28-29]. For the least reliability resources, this study showed the lack of confidence in the state media including social medias, television, and websites. Several aspects of government communication may have contributed to the lack of confidence, including a lack of transparency about vaccine options and perceived favoritism toward certain manufacturers. A study among Thai seniors found that high vaccine hesitancy was linked to a lack of confidence in the healthcare system's ability to treat COVID-19, distrust in certain vaccine manufacturers, and being offered a vaccine from an unexpected manufacturer[25]. Limited information on available vaccine options from the governmental organization could influence public willingness to get vaccinated. This finding suggest that it is important for the government to build trust in the public to improve the vaccine acceptance among the population. Strategies to build trust include enhancing transparency by providing clear, detailed information about the vaccines, addressing public concerns and misconceptions, and actively engaging with the community to bridge the gap between the government and the public. Our study could place more emphasis on the practical guidelines for educational campaigns to enhance vaccine acceptancy in Thai pregnant women. Unified information dissemination across Thailand is crucial for improving public understanding. Consistent online health literacy promotion could accelerate COVID-19 vaccine acceptance. Educational campaigns should address vaccine safety in pregnant women and the risks of severe complications due to COVID-19 without vaccination. Community leaders and health professionals can engage with the public to answer common questions, address concerns, and dispel misconceptions about COVID-19 and vaccines.

Our study has some limitations. First, this was a pilot study to determine vaccine acceptance in pregnant women, who are a high-risk group for adverse outcomes after contracting COVID-19[30], and the sample size was small. This could affect the representativeness of results to a broader population and limit the ability to detect accurate trends or patterns in vaccine acceptance or hesitancy. Second, most of the pregnant women who responded to this questionnaire resided in Bangkok, which may limit the generalizability of the results. Since the study relied on a convenience sample and most of the respondents were from Bangkok, the findings may be specific to this particular group and may not be applicable to a broader or different population, such as women living in remote or rural areas. Third, a small number of women declined to answer some questions, although these questions regarded sociodemographic characteristics, not vaccine acceptance. This could introduce bias and underrepresent certain views and characteristics, particularly from sociodemographic groups with a low response rate. Future studies should clearly explain the importance of these questions and provide assurances of confidentiality to encourage participation. Fourth, the number of new cases per

day, as well as the efficacy and safety data of COVID-19 vaccines against newly emerged SARS-CoV-2 variants, could change overtime. This constantly evolving data could ultimately shift vaccine hesitancy rates, therefore potentially skewing the results. These factors could influence the vaccination decisions and should be assessed in a timely manner. Future studies should use longitudinal designs to regularly update vaccine efficacy and safety information, including follow-up surveys to track changes in perceptions and hesitancy. Time-dependent factors, such as new COVID-19 variants or updated vaccine evidence, should be communicated to the public, with studies capturing these changes over time. Additional qualitative research could provide deeper insights into vaccine hesitancy. Expanding sample sizes by recruiting from multiple sites or extending study duration can improve participant numbers. Combining questionnaires with interviews in a mixed-methods approach could enhance understanding of vaccine hesitancy and increase study representativeness and statistical power. Lastly, the associations observed in our study are from an observational study and therefore subject to unobserved confounding.

Conclusion

Through the newly developed questionnaires which aim to obtain comprehensive relevant information and analyze all possible barriers in a Thai context, this study pinpointed modifiable barriers to COVID-19 vaccination in pregnant individuals including inadequate knowledge on COVID-19 disease and vaccines, and mistrust in the government media. To enhance vaccine acceptance, public health interventions should focus on vaccine safety and the risks of severe COVID-19 complications without vaccination. The government should build public trust and engage with the public through community leaders and health professionals to address questions, concerns, and misconceptions. These efforts are crucial for increasing vaccine coverage among Thai pregnant women.

Acknowledgements

We would like to thank the staff at the antenatal care clinics for their assistance in distributing the questionnaires.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 77-81.

CASE REPORT

Idiopathic Gestational Gigantomastia: A case report

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ABSTRACT

Background: Gestational gigantomastia (GGM) is described as a diffuse and rapid enlargement of the breasts during pregnancy. It is a rare condition with an incidence of 1 in 28,000 to 1 in 100,000 pregnancies worldwide.

Case presentation: We present a case of a 29-year-old lady, G_2P_1 at 15 weeks gestation who presented with 2-months history of painful bilateral breast swelling. Clinical examination revealed erythematous bilateral breast enlargement. Results of multiple breast biopsies range from lactational adenoma and acute on chronic mastitis changes. She was treated with multiple courses of antibiotics for bilateral cellulitis with mastitis, however both breasts continued to enlarge. The revised diagnosis of gestational gigantomastia was made and she was started on steroid. Nevertheless, she failed to respond. Oral Bromocriptine commenced at 29 weeks showing some reduction in her breasts size. The fetus was however found to have a growth restriction requiring delivery at 37 weeks. Her breast has reduced by half of the initial volume during postnatal review. She was offered bilateral reductive mammoplasty and mastopexy, but she was not keen and opted for conservative management.

Conclusion: A thorough investigation is necessary to rule out other causes in women presenting with gigantomastia in pregnancy. GGM treatment ranges from conservative, hormonal therapy, reduction mammoplasty, mastectomy with or without reconstruction. This depends largely on the severity of disease and the patient's wish.

Keywords: gestational gigantomastia, mastitis, breast reduction, mastopexy.

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Received: 5 August 2024, **Revised:** 28 September 2024, **Accepted:** 18 October 2024

Introduction

Gestational gigantomastia (GGM) is characterized by a rapid excessive and disproportionate enlargement of the breasts during pregnancy. There is no objective definition of GGM worldwide from literature search, some suggest the quantification of GGM is based on the weight of removed breast tissue when surgery is performed, however this was not widely accepted[1,2]. It is occasionally associated with ulceration, infection, and necrosis of the overlying skin. It is a rare condition with an incidence of 1 in 28,000 to 1 in 100,000 pregnancies worldwide[3]. The etiology of GGM is still uncertain with many proposed theories. GGM has been reported to be associated with a response of breast receptors to gestational hormones and with hyperprolactinemia. It causes physical and psychological problems that severely affect the patient's quality of life. A thorough workup including serum markers for infection, electrolytes, hormonal profile and tissue biopsy should be done in order to rule out other causes in women presenting with gigantomastia in pregnancy. Treatment ranges from conservative hormonal therapy, reduction mammoplasty, mastectomy with or without reconstruction.

Case report

We present a case of a 29-year-old lady, G_2P_1 at 15 weeks gestation presented with 2-months history of painful bilateral breast swelling for the past 5 weeks. She was breastfeeding her first child when she embarked into this pregnancy and has stopped breastfeeding once this pregnancy was confirmed at 10 weeks gestation. She reported her original breast size was a B cup and denied similar problems during her first pregnancy. Her obstetric history includes previous caesarean section for dysfunctional labor at term.

Her height was 155 cm with a weight of 47 kg, making her BMI 19.56 kg/m^2 during her first presentation. Clinical examination revealed non tender erythematous bilateral breast enlargement (Fig. 1), in which she required a D cup size. She was initially treated with multiple courses of antibiotics for bilateral cellulitis with mastitis. Ultrasonography of the breasts did not reveal any underlying suspicious lesions. During her second visit at 18 weeks, her breasts continued to enlarge (Fig. 2) and became more inflamed despite multiple courses of antibiotics. Hence, the breast surgeon decided to perform biopsy to exclude inflammatory breast carcinoma. As there was no specific target or focus lesion identified on ultrasound, several punch biopsies were taken randomly from both inflamed looking breasts ensuring the whole thickness of dermis and subcutaneous layer were captured. Fortunately, the biopsies results range from lactational adenoma and acute on chronic mastitis changes. Blood parameters and hormonal profile, including estrogen, progesterone and prolactin levels were within normal limit of pregnancy values. The pain and erythema improved with the antibiotics, however both breasts continued to enlarge excessively throughout the pregnancy, in which she could not even wear a bra of her suitable size from 22 weeks gestation onwards (Fig. 3). This rapid growth resulted in back pain and difficulty in movement. The revised diagnosis of gestational gigantomastia was made and she was started on steroid. Nevertheless, she failed to respond. Oral bromocriptine 2.5 mg once daily was commenced at 29 weeks and there was some reduction in her breast size, hence it was continued.

During the treatment course, the fetus was found to have asymmetrical fetal growth restriction (FGR) at 34 weeks with normal amniotic fluid volume and Doppler study. She was otherwise normotensive, with no other risk factor for FGR. She subsequently delivered a healthy female baby weighing 2,100 grams at 37 weeks gestation via caesarean section. She declined the continuation of bromocriptine as she was keen to breastfeed her baby. Follow-up at 6 weeks postpartum showed her breast volume has decreased to about half of the enlarged volume and has become severely ptotic (Fig. 4). Unfortunately, due to the still excessively enlarged breast, she was unable to breastfeed her baby. Review at 3 months postpartum showed her breast size has reduced to D cup size but

remained ptotic. She was counselled for bilateral reductive mammoplasty and mastopexy by the breast surgeon but she declined as she was still able to endure her symptoms.

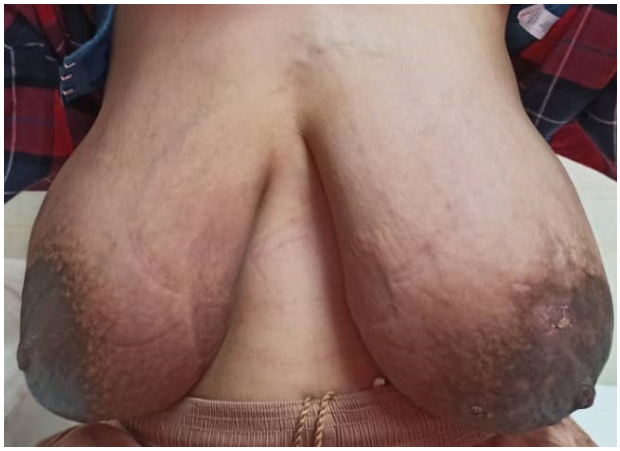

Fig. 1. Photograph showing bilateral gigantomastia at 15 weeks (initial presentation).

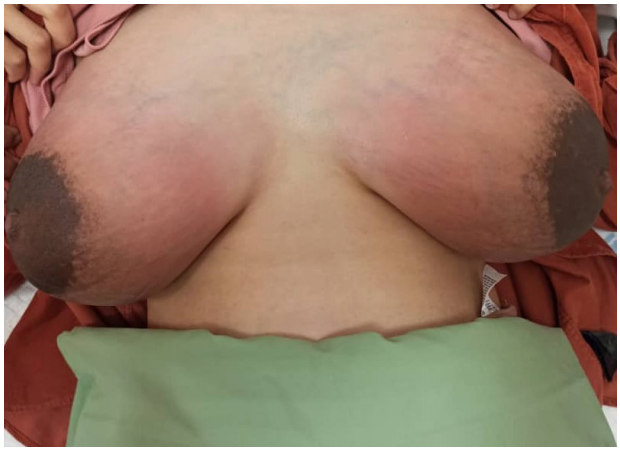

Fig. 2. Photograph showing gestational gigantomastia complicated with cellulitis at 18 weeks.

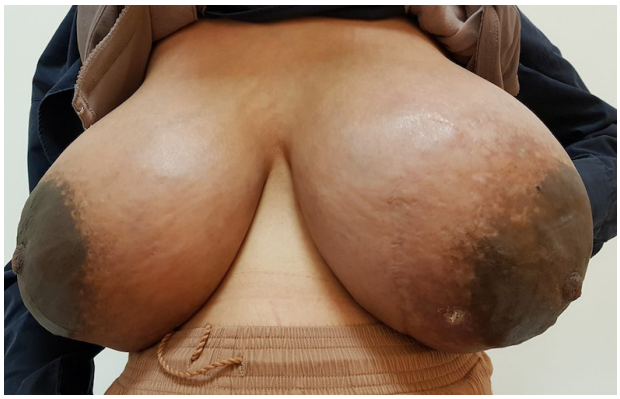

Fig. 3. Photograph showing bilateral breasts continue to enlarge with left breast ulceration at 22 weeks.

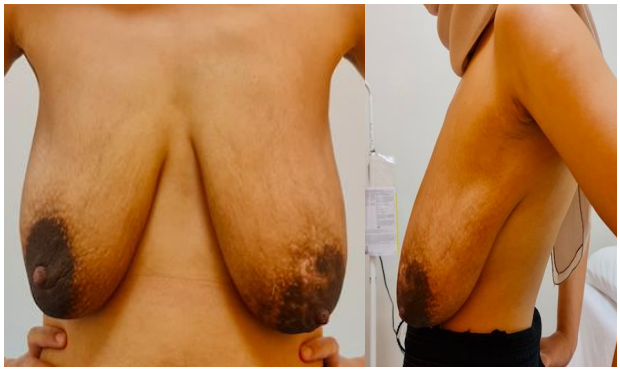

Fig. 4. Photograph showing reduction in size of bilateral breasts at 6 weeks postpartum.

Discussion

GGM has been documented to have associations with several conditions including hormonal imbalances such as hyperprolactinemia, hypercalcemia, deranged liver function tests, autoimmune diseases like systemic lupus erythematosus, and underlying malignancy[5,6,7]. Certain medications have also been reported to have associations with GGM such as prednisolone, D-penicillamine and cortisone[8,9,10]. However, the mechanism of action on how these drugs causes GGM remains unclear. Nevertheless, there have been limited cases which reported such associations; hence it may not be a direct causal relationship. Therefore,

the workup for GGM should focus on identifying these potential associations. Basic laboratory investigations including full blood count to look for white cell count and systemic inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), estrogen, progesterone, prolactin and testosterone level should ideally be evaluated[6]. In addition to the laboratory tests, breast ultrasound scan or magnetic resonance imaging (MRI), and breast biopsies may be obtained to exclude underlying malignancy as performed in this case[6]. Other disease processes must be considered before making a diagnosis of benign GGM. This comprises of both benign conditions; infectious mastitis, juvenile breast hypertrophy, fibrocystic change or fibroadenoma and/or normal pregnancy-related breast enlargement and malignancy. Rapid breast enlargement with axillary swelling may mimic malignancy. Other signs such as oedema and peau d'orange skin changes consistent with inflammatory carcinoma need to be excluded via cytomorphological evaluation[3,4].

GGM, although benign, can be a significantly debilitating disease. It does not only result in physical complications if left untreated but also affects emotional and social incapacity. It is important to recognize it early to ensure treatment can be started as soon as possible to prevent future complications. Conservative measures include suitable brassiere support, proper skin hygiene, and analgesia[4,5]. During pregnancy, medical management is often preferred over surgical management due to the risk of fetal harm, although the latter may be pursued in the case of massive hemorrhage, ulceration or sepsis[4,5,11]. Women diagnosed with GGM should ideally be seen more frequently by both the obstetricians and breast surgeons to identify for any ulceration, necrosis or hemorrhage. Fatal cases of hemorrhage and sepsis from GGM due to partially treated ulcers have been reported[7,8,12].

Bromocriptine, a dopaminergic agonist, has been the medication of choice for GGM[3,5,13]. It has been shown to reduce breast size and suppress lactation while allowing surgical intervention if desired[3,5,10]. Bromocriptine is found to be safe in pregnancy with no teratogenic risk to the fetus. It has been safely used in pregnant women with pituitary prolactinoma[9]. Nevertheless, maternal blood pressure and fetal growth require close monitoring due to hypothetical risk of hypertension and fetal growth restriction as described in this case. Ideally, bromocriptine is continued throughout pregnancy and in the postpartum period to reduce breast size, to allow for surgical intervention when preferred[3,10]. Surgical approaches, including reduction mammoplasty and mastectomy are warranted when medical treatment fails, or patient develops debilitating symptoms[4,6,13]. Since there is a possibility of recurrence with simple mastectomy or reduction mammoplasty, bilateral mastectomy with reconstruction may be the treatment of choice in women who desire future pregnancies[4,6].

Conclusion

GGM is a rare disorder with many potential complications, all of which may lead to a significant reduction in the quality of life. Other various benign and malignant diseases should be ruled out through endocrinology and histopathologic evaluation. Treatment is often pharmacological throughout pregnancy and in the early postpartum period, although the definitive treatment is surgical. Fetal growth should be monitored with bromocriptine therapy due to case reports describing fetal growth restriction. Knowledge on this rare condition is necessary especially for obstetricians, whom will be the first line seeing these women.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Thai Journal of Obstetrics and Gynaecology
January 2025, Vol. 33, No. 1, pp. 82-86.

CASE REPORT

Intratumor Hemorrhage in Pedunculated Subserosal Leiomyoma Mimic Intraabdominal Bleeding: A case report

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ABSTRACT

A 43-year-old para 2-0-0-2 woman with a history of three cesarean sections and tubal sterilization presented with chronic pelvic pain and heavy menstrual bleeding due to a large subserous myoma (16 x 9 cm). Two months after the initial presentation, she was admitted to the emergency department with acute abdominal pain and dyspnea. Physical examination revealed a distended abdomen, generalized tenderness, and a 24-week-sized mass. Laboratory tests indicated anemia with a hemoglobin level of 8.8 g/dl. Transabdominal ultrasound and contrast-enhanced computed tomography (CT) identified significant free fluid in the abdominal cavity and a large exophytic uterine mass, suspected to be a pedunculated subserous myoma. Exploratory laparotomy confirmed 500 mL of intraperitoneal serosanguinous fluid and a pedunculated subserous myoma measuring 27 cm, with evidence of intra-tumor hemorrhage. A total abdominal hysterectomy with bilateral salpingectomy was performed, with six units of packed red blood cells transfused. Pathological examination confirmed a subserous leiomyoma with hemorrhage and congestion. This case illustrated the rare complication of intra-tumor hemorrhage with intraperitoneal fluid reaction, typically presenting as acute abdominal pain. Emergency surgery was required for diagnosis and management, especially in the absence of trauma.

Keywords: intraabdominal bleeding, subserous leiomyoma, intratumor hemorrhage.

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Received: 13 September 2024, **Revised:** 1 October 2024, **Accepted:** 4 November 2024

Introduction

Leiomyomas (known as myomas or uterine fibroids) are common benign tumor in reproductive aged women. Leiomyomas are clonal neoplasms of the uterus and have both smooth muscle and fibroblast components[1,2]. The clinical presentation of leiomyoma is variable, ranging from asymptomatic patient to those with recurrent, progressive symptoms that affect a women's daily activities[3]. The most common symptoms are menorrhagia (heavy menstrual bleeding) and dysmenorrhea (menstrual pain)[4].

The International Federation of Gynaecology and Obstetrics (FIGO) classification system for uterine leiomyomas classifies leiomyomas based on location. The FIGO scale ranges from 0 to 8, according to their location in the uterus[5]. Infrequently, leiomyomas cause acute complications. The complications include thromboembolism, acute torsion of subserosal pedunculated leiomyomata, acute urinary retention and renal failure, acute pain caused by red degeneration during pregnancy, acute vaginal or intraperitoneal hemorrhage[6].

However, the subserous leiomyoma may cause a very rare complication. Acute torsion of subserous leiomyoma lead to ischemic gangrene and peritonitis is very rare[7]. Intra-leiomyoma hemorrhage and intratumor bleeding are extremely rare[8,9]. This case report described a case of acute abdominal pain and intraperitoneal fluid resulting from intratumor hemorrhage of pedunculated subserous leiomyoma.

Case report

A 43-year-old, para 2-0-0-2 woman, known case of huge intramural and subserosal myoma (FIGO type 6) (size 16 x 9 cm) came to the present hospital with chronic pelvic pain and heavy menstrual bleeding 6 months earlier. She had a regular 25-30 days' cycle and dysmenorrhea. She was an unremarkable past history except history of 3 repeat cesarean sections with tubal sterilization. Laboratory investigations revealed a hemoglobin level was 10.6 g/dl, a mean corpuscular volume (MCV) 82.1 fl, and a white blood cells 13.10 x 103/ul. She was advised to undergo hysterectomy.

About 2 months later, she presented to the emergency room with acute abdominal pain and dyspnea for 6 hours. Her menstrual period started 2 days ago. She denied trauma and other respiratory symptoms.

On physical examination, she was afebrile, a pulse rate was 90 beats per minute, blood pressure was 154/64 mmHg, and respiratory rate was 22 beats per minute. The abdominal examination revealed a distended abdomen with generalized tenderness, guarding and rebound. A 24-week sized mass was palpated. Laboratory investigation highlighted anemia (hemoglobin level 8.8 g/dl, MCV 72.2 fl, white blood cells 22.63 x 103/ul). Transabdominal ultrasonography disclosed free fluid in pelvic cavity, hepatorenal and splenorenal pouch and a 15 x 13 cm fundal subserosal leiomyoma. Transvaginal ultrasound revealed normal both ovaries. Emergency computed tomography (CT) was performed for further evaluation. A contrast CT whole abdomen showed large non-enhancing exophytic mass arising from uterine fundus, possibly pedunculated subserous myoma, moderate amount of free fluid at perihepatic, perisplenic, bilateral paracolic gutter and pelvic regions but no evidence of other internal organ injury (Fig. 1).

Based on clinical, laboratory and imaging findings, the provisional diagnosis was intraperitoneal bleeding originating from the uterine myoma or a torsion of subserous myoma. Therefore, the patient was performed an exploratory laparotomy. The findings revealed 500-ml intraperitoneal serosanguinous fluid and a large rubbery reddish dark brown pedunculated subserous myoma at fundus, which measured approximately 27 cm in maximum diameter, with no identifiable bleeding site (Fig. 2). Total abdominal hysterectomy with bilateral salpingectomy was performed. Total six units of packed red blood cell transfused. Estimated blood loss from the operation was about 600 ml. The patient had an unremarkable postoperative course and was discharged on postoperative day 4.

A pathological examination revealed a 22.0 x16.0 x11.0 cm subserous mass at the fundus. Microscopic examination showed spindle cells with hemorrhage and congestion.

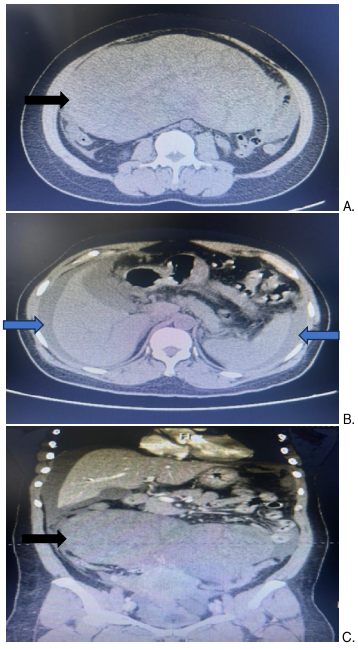

Fig. 1. Contrast computed tomography whole abdomen. (A, C) large non-enhancing exophytic mass arising from uterine fundus, possibly pedunculated subserous myoma : black arrow. (B) moderate amount of free fluid : blue arrow shows perihepatic and perisplenic free fluid

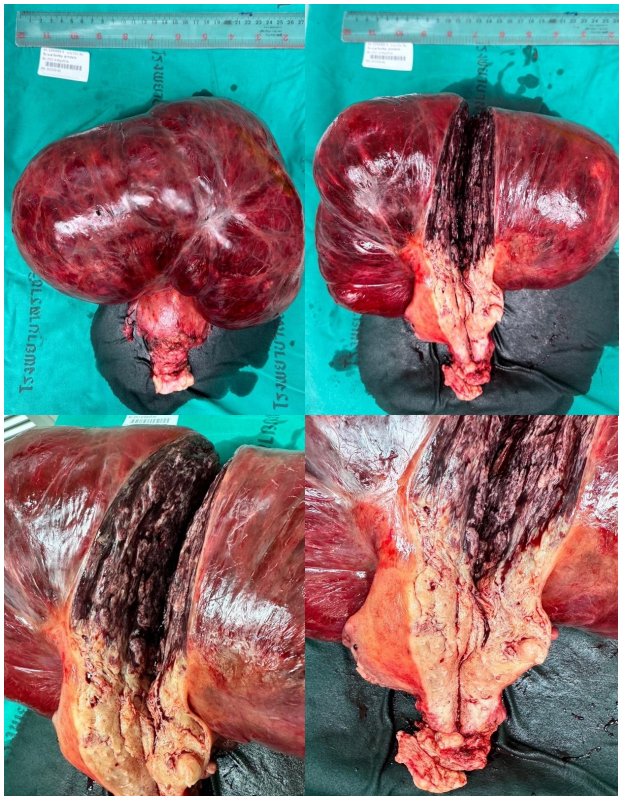

Fig. 2. Gross findings, large rubbery reddish dark brown peduculated subserous myoma at fundus.

Discussion

The complications of subserous leiomyoma include torsion or rupture, red degeneration and intratumor hemorrhage are extremely rare. The majority presents as acute abdominal pain[6]. There are a few case reports of intraperitoneal hemorrhage form myoma without trauma such as bleeding from spontaneous rupture of myoma(10), ruptured vessels overlying a uterine myoma[11-13].

The occurrence of intraperitoneal fluid or hemorrhage suggests an abdominal organ injury such as perforation or ischemia. While definite diagnosis of intraperitoneal bleeding associated with myoma is unlikely. The usual preoperative differential diagnosis may be shifted the focus to twisted adnexa or other internal organ injury. The imaging, ultrasound and CT are diagnostic tools for myoma and its suspected complications, but it is difficult to detect the site of bleeding by imaging alone.

In the present case, patient visited the emergency room with the chief complaint of acute abdominal pain. Intraperitoneal ascites was identified, and the transfusion of blood was needed due to anemia suspected from intraabdominal bleeding. This presenting symptom was similar to the presenting symptoms from the previous report by Akahira et al[12] and Mattison et al[13]. These findings were often misdiagnosed as internal organs ruptured. An

emergency laparotomy was performed. The finding showed an edematous pedunculated submucous myoma with intra-leiomyoma hemorrhage which was similar to the previous report from Manopunya et al[8] and Koide et al[14], but these two case reports occurred during postpartum period. And systematic review from Lim et al[15] indicated that intraperitoneal fluid associated with uterine myoma was causes by the rupture of superficial blood vessels (60.8%), ruptured fibroids (27.25%), and fibroid avulsion (8%). Another study[16], however, has shown that intraperitoneal fluid is not always due to bleeding but may result from the release of inflammatory cytokines and growth factor, which increase vascular permeability. This creates an imbalance in arterial flow, venous drainage and direct pressure of the fibroid mass on lymphatic vessels, consistent with our findings, where no cause of bleeding was identified.

Intratumor hemorrhage with peritoneal fluid can cause serious and emergent conditions. In most cases that occur during pregnancy period, it is believed that the size of uterine myoma increases due to rising estrogen levels and increased blood flow. However, it is extremely rare for this to occur in non-pregnancy women. Contributing factors implicated in this complication may include increased abdominal pressure or torsion, which can result in the compression of feeding vascular flow, leading to myoma swelling and edematous changes. In this case, we hypothesized that venous return from the tumor had been compressed during partial torsion of myoma[8,14].

Surgical exploration and removal of a pedunculated subserosal myoma are typically performed when complications related to myoma are suspected. Nevertheless, based on the serious consequences of intraperitoneal hemorrhage in huge tumors and the possibility of intratumor hemorrhage, as observed in our case, a hysterectomy was deemed necessary, especially as fertility preservation was not a concern[6,8,17].

Conclusion

Intratumor hemorrhage of myoma in non-pregnancy woman is extremely rare complication. However, the presenting symptoms may mimic with intraabdominal bleeding. Thus, it needs prompt intervention, so it is important to keep in mind the possibility of subserous myoma with complication.

Potential conflicts of interest

The authors declare no conflicts of interest.

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