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## EDITORIAL

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

Vorapong Phupong, M.D., FRTCOG.\*

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

This third issue of Thai Journal of Obstetrics and Gynaecology 2026 contains many interesting articles. The special article is “Maternal iodine requirements in pregnancy and lactation: Critical roles and monitoring strategies.” The topics included iodine metabolism during pregnancy and lactation, excessive iodine intake, assessment of iodine status, sources of iodine, and impact of iodine deficiency<sup>(1)</sup>.

This issue also contains seven original articles. Deepthi et al performed a case-control study to characterize biochemical, hormonal, and inflammatory alterations in endometriosis. The results showed prolactin and interleukin-6 as the strongest diagnostic predictors, while multivariable analysis confirmed body mass index, abdominal circumference, prolactin, and interleukin-6 as key factors associated with endometriosis<sup>(2)</sup>.

Limsawan et al performed a secondary analysis on a previous prospective diagnostic single-center study to evaluate the diagnostic performance of the International Ovarian Tumor Analysis (IOTA) simple rules in combination with serum tumor marker cancer antigen 125 (CA125). They found the IOTA simple rules achieved an area under the curve (AUC) of 0.938. The IOTA simple rules along with subjective assessment demonstrated a similar AUC, 0.933. Integrating CA125 with the IOTA simple rules reduced the AUC to 0.825<sup>(3)</sup>.

Nakapun et al performed a double-blind, randomized, placebo-controlled trial to evaluate the short-term efficacy of a multi-strain probiotic supplement (Bifidobacterium longum, B. breve, B. lactis, B. animalis TA1, Lactobacillus paracasei MSMC 39-1, L. rhamnosus, L. reuteri TF314, and L. gasseri) in improving bowel movement frequency, stool consistency, and menopause-related quality of life in women with functional constipation. They found a 4-week multi-strain probiotic treatment demonstrated improvements in the frequency of bowel movements, physical domain and total score of menopause-related quality of life<sup>(4)</sup>.

Puenprom et al performed a randomized, double-blind, placebo-controlled trial to evaluate the effect of oral ginger supplementation, in combination with early maternal oral feeding, on breast milk volume in women undergoing scheduled cesarean section. The results showed oral ginger supplementation combined with early maternal oral feeding significantly increased breast milk volume and shortened the time to the onset of lactation in women following scheduled cesarean section<sup>(5)</sup>.

Sintrakulchai et al performed a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness and safety of topical 2% lidocaine gel versus a placebo for post-episiotomy analgesia, assessed

using the numeric rating scale pain scores at 6, 12, and 24 hours postpartum. They found topical 2% lidocaine gel did not provide a statistically significant reduction in post-episiotomy perineal pain during the first 24 hours compared with placebo<sup>(6)</sup>.

Jindaluang et al performed a double-blinded randomized controlled trial to determine the efficacy of tranexamic acid (TXA) in reducing intraoperative blood loss in difficult abdominal hysterectomy for benign gynecological disease. The result showed preoperative intravenous TXA did not reduce blood loss in cases of difficult abdominal hysterectomy for benign gynecological disease<sup>(7)</sup>.

Wangsri et al performed a combined retrospective-prospective cohort study to determine the incidence of preeclampsia and pregnancy outcome in women diagnosed with gestational hypertension (GH) at Chonburi Hospital. They found 25.7% preeclampsia progression to GH. The risks of preeclampsia progression were early gestational age of GH diagnosis and high diastolic blood pressure at diagnosis. Adverse pregnancy outcomes in preeclampsia women were preterm delivery and high cesarean section rate<sup>(8)</sup>.

The Royal Thai College of Obstetricians and Gynaecologists midyear meeting already held during 21 - 24 April 2026 at Centara Grand at Central Plaza Ladprao, Bangkok, Thailand. The theme of the meeting is "Redefining the Future of Women's Health." This meeting was successful with 800 delegates.

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## SPECIAL ARTICLE

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# Maternal Iodine Requirements in Pregnancy and Lactation: Critical roles and monitoring strategies

Arissara Kuptarak, M.D.\*,  
Vorapong Phupong, M.D., FRTCOG.\*

\* Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

### ABSTRACT

Iodine plays a vital role in fetal neurodevelopment and is closely linked to thyroid function in both mothers and infants. Iodine deficiency during pregnancy is associated with adverse obstetric outcomes, impaired fetal growth, and in severe cases, can result in neonatal cretinism. An adequate iodine status in pregnancy is defined by a median urinary iodine concentration of 150–249 µg/L. Several methods are available to assess iodine sufficiency in pregnant and lactating women, each with its own strengths and limitations. These include urinary iodine concentration, serum iodine levels, serum thyroglobulin, breastmilk iodine concentration, neonatal thyroid-stimulating hormone levels, and thyroid volume assessment. While iodine supplementation is crucial in deficiency states, excessive iodine intake can also disrupt thyroid function, potentially leading to either hyperthyroidism or hypothyroidism. Therefore, monitoring and maintaining appropriate iodine levels during pregnancy and lactation is essential for maternal and neonatal health.

**Keywords:** iodine, prenatal, lactation, iodine assessment, urinary iodine, serum iodine, breastmilk iodine.

**Correspondence to:** Vorapong Phupong, M.D., FRTCOG, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Email: vorapong.p@chula.ac.th

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## Introduction

Iodine is one of the minerals that required during pregnancy<sup>(1)</sup>. The recommended dietary allowance (RDA) for iodine is in the range of 0.20 to 0.25 milligrams/day, slightly varying between recommendations<sup>(1)</sup>. Iodine is an essential nutrient for the production of thyroid hormones in pregnant women and infants. It is also important for the development

of the nervous system. A deficiency in prenatal iodine can lead to childhood intellectual disability and autism<sup>(2)</sup>. Risks of miscarriage, preterm labor, low birthweight, preeclampsia and stillbirth are increased in iodine deficiency during pregnancy. Moreover, iodine deficiency remains a leading contributor to the development of maternal hypothyroidism<sup>(3)</sup>. The increased iodine requirement during pregnancy is

primarily attributed to the need to maintain maternal euthyroid, facilitate transplacental transfer of thyroid hormones to the fetus, and compensate for enhanced renal iodine clearance<sup>(4)</sup>.

Insufficient iodine intake during lactation can hinder maternal thyroid hormone production, potentially disrupting the infant's physical, neurological, and cognitive development. When maternal iodine levels are inadequate, the iodine content in breast milk decreases, directly limiting the iodine supply available to exclusively breastfed infants. Inadequate iodine during the early postnatal period—especially within the first six months—can lead to significant impairments in cognitive and psychomotor development, which may not be fully reversible even if iodine status is corrected later<sup>(5)</sup>.

Iodine deficiency has emerged as a major global health concern, affecting approximately 2 billion individuals worldwide<sup>(6)</sup>. The Iodine Global Network (IGN) 2024 annual report identified 21 countries as having insufficient iodine levels, while Thailand was classified as a country with adequate iodine status<sup>(7)</sup>. However, a study conducted in northern Thailand revealed that nearly 44% of pregnant women exhibited insufficient iodine levels<sup>(8)</sup>. Moreover, research from Bangkok reported that 58% of lactating women had breast milk iodine concentrations below 150 µg/L, suggesting inadequate iodine intake to meet the nutritional needs of their infants<sup>(9)</sup>.

Importantly, iodine deficiency is largely preventable through adequate dietary intake and appropriate supplementation. The Institute of Medicine (IOM) has set the daily recommended dietary allowance (RDA) at 220 micrograms for pregnant women and 290 micrograms for those who are breastfeeding<sup>(10)</sup>. According to the World Health Organization (WHO), a median urinary iodine concentration (UIC) ranging from 150 to 249 µg/L indicates adequate iodine status in pregnant women. However, in lactating women, a lower median UIC of 100 µg/L is considered sufficient, as a significant proportion of iodine is secreted into breast milk to support the infant's nutritional requirements<sup>(11)</sup>.

Because individual iodine intake fluctuates significantly throughout the day and between days, median UIC thresholds are not considered reliable indicators of an individual's long-term iodine status<sup>(12)</sup>. As for the concentration of iodine in breast milk, the adequate level should range between 150 and 180 µg/L<sup>(13)</sup>. This article provides an overview of the significance of sufficient iodine intake during pregnancy and lactation, methods for assessing prenatal and lactating iodine status, dietary sources of iodine, and the potential consequences of iodine deficiency in pregnancy.

### ***Iodine metabolism during pregnancy and lactation***

During pregnancy, maternal iodine requirements increase by approximately 50%, primarily due to several physiological adaptations. These include an elevated renal clearance of iodine resulting from an increased glomerular filtration rate, augmented maternal thyroid hormone synthesis to meet both maternal and fetal metabolic demands, and the transplacental transfer of iodine to the fetus—particularly significant during the second and third trimesters, when fetal thyroid hormone production is initiated. Furthermore, in the first trimester of gestation, the fetus relies entirely on maternal thyroxine (T<sub>4</sub>), as the fetal thyroid gland does not attain functional maturity until around the 12<sup>th</sup> week of pregnancy<sup>(14)</sup>.

In the human gastrointestinal tract, iodine is converted to iodide, with over 90% being efficiently absorbed in healthy adults. After entering the circulation, iodide is primarily taken up by the thyroid gland or eliminated via renal excretion. While renal clearance remains relatively constant, thyroidal uptake varies depending on iodine status and dietary intake. Under conditions of adequate iodine supply, the thyroid absorbs less than 10% of circulating iodide; however, in cases of chronic iodine deficiency, uptake can exceed 80%. With the kidneys excrete over 90% of ingested iodine via urine, urinary iodine concentration serves as a promising biomarker for assessing iodine deficiency<sup>(15)</sup>.

Regarding neonatal iodine metabolism, a marked physiological surge in serum thyroid-

stimulating hormone (TSH) occurs within 30 to 60 minutes after birth, reaching levels of approximately 60–80 mIU/mL as the newborn adapts to life outside the womb. This surge declines rapidly, with TSH concentrations stabilizing within 3 to 5 days postpartum. The transient elevation in TSH stimulates the synthesis of T4 and triiodothyronine (T3), which peak around 24 hours after birth and gradually decrease to more stable levels by days 5 to 7. This downward trend continues throughout infancy and childhood, albeit more slowly. Notably, T4 turnover in infancy is significantly increased, with infants producing roughly three times more T4 per kilogram of body weight than adults. However, neonates are born with minimal iodine stores—approximately 300 µg—which are rapidly depleted within a few days. Consequently, an adequate external supply of iodine, primarily through breast milk or infant formula, is critical to support the elevated thyroid hormone demands during early development<sup>(5)</sup>. Infants exhibit reduced iodine clearance compared to adults, primarily due to the immaturity of their renal function<sup>(16)</sup>. During lactation, iodine is actively transported into breast milk by the sodium/iodide symporter in the mammary gland, ensuring sufficient iodine availability to maintain healthy thyroid function and support continued neurological development<sup>(17)</sup>.

### Excessive iodine intake

Excess iodine intake can trigger the Wolff-Chaikoff effect, which reduces thyroid hormone synthesis by inhibiting thyroid peroxidase<sup>(18)</sup>. In some vulnerable individuals, especially fetuses and newborns, failure to escape the acute Wolff–Chaikoff effect may result in iodine-induced hypothyroidism, which may be either short-term or permanent<sup>(14)</sup>. Conversely, excessive iodine intake may also induce the Jod-Basedow phenomenon, characterized by iodine-induced thyrotoxicosis. This condition is more frequently observed in individuals with preexisting thyroid abnormalities, such as nontoxic nodular goiter or euthyroid Graves' disease, and in populations residing in iodine-deficient regions<sup>(19)</sup>.

According to the WHO classification, a median UIC between 250 and 499 µg/L indicates more than adequate intake, while a median UIC of 500 µg/L or higher is considered excessive<sup>(11)</sup>. A prior systematic review reported that 52% of the 10,736 pregnant women from various regions worldwide had excessive iodine levels. Among these studies, 66.6% reported cases of hypothyroidism in the pregnant women, while hyperthyroidism was reported in 0.6% to 19.7% of the studies<sup>(20)</sup>.

Currently, there is evidence from various guidelines regarding iodine intake during pregnancy and lactation, as depicted in Table 1.

**Table 1.** Daily iodine intakes and tolerable upper intake levels for pregnant and lactating women<sup>(10, 21, 22)</sup>.

|                 | Daily iodine intake (µg/day) |     | Tolerable upper intake level (µg/day) |      |
|-----------------|------------------------------|-----|---------------------------------------|------|
|                 | IOM                          | WHO | IOM                                   | EFSA |
| Pregnant women  | 220                          | 250 | 1,100                                 | 600  |
| Lactating women | 290                          | 250 | 1,100                                 | 600  |

IOM: the institute of medicine, WHO: world health organization, EFSA: european food safety authority.

### Assessment of iodine status

#### Urinary iodine concentrations

Urinary iodine is a reliable indicator of recent dietary iodine intake, since over 90% of consumed iodine is eliminated through the kidneys within 24 to 48 hours after ingestion<sup>(23)</sup>. Due to daily

fluctuations in urinary iodine excretion, accurately determining an individual's iodine status with 20% precision requires collecting either 10 spot urine samples or 10 individual 24-hour urine samples from pregnant women<sup>(24)</sup>.

Urinary iodine concentration is measured

using either the colorimetric Sandell-Kolthoff method or inductively coupled plasma mass spectrometry (ICP-MS)<sup>(5)</sup>. Generally, a minimal urine volume (0.5–1.0 mL) is sufficient for UIC analysis. However, UIC reflects recent iodine intake

at the time of collection, whereas thyroid size serves as a longer-term biomarker, indicating iodine status over several months or years<sup>(25)</sup>. Table 2 presents the UIC cut-off values that indicate health significance for pregnant and lactating women.

**Table 2.** Criteria for evaluating iodine status using median urinary iodine concentration (UIC) values<sup>(11)</sup>.

| Population      | Median UIC (µg/L) | Iodine intake status |
|-----------------|-------------------|----------------------|
| Pregnant women  | < 150             | Insufficient         |
|                 | 150 - 249         | Adequate             |
|                 | 250 - 499         | Above requirements   |
|                 | ≥ 500             | Excessive            |
| Lactating women | < 100             | Insufficient         |
|                 | ≥ 100             | Adequate             |

In some cases, UIC is adjusted for urinary dilution using creatinine concentration (expressed as

UIC/Cr) to improve assessment reliability. The formula is shown below<sup>(26)</sup>.

• 
$$\text{UIC/Cr (}\mu\text{g/g creatinine)} = \frac{\text{UIC from spot urine sample}}{\text{Urinary creatinine concentration}}$$

During pregnancy, the glomerular filtration rate increases, leading to a higher urine output over a 24-hour period and resulting in dilution of the urine. Consequently, UIC tends to decrease; however, this reduction does not necessarily reflect a true iodine deficiency. A study conducted in China suggested that the UIC/Cr ratio is a more reliable indicator of iodine status in pregnant women

compared to UIC, as it reduces variability caused by differences in urine volume and dilution. The area under the receiver operating characteristic (ROC) curve for the UIC/Cr ratio was 0.92 for identifying iodine deficiency and 0.75 for detecting excessive iodine levels<sup>(27)</sup>. The reference intervals for the UIC/Cr ratio in pregnant women are presented on Table 3.

**Table 3.** The reference intervals for the urinary iodine-to-creatinine (UIC/Cr) ratio in pregnant women<sup>(28)</sup>.

|               | First trimester | Second trimester | Third trimester |
|---------------|-----------------|------------------|-----------------|
| UIC/Cr (µg/g) | 38.63 - 489.46  | 58.48 - 644.03   | 56.27 - 644.93  |

Twenty-four-hour urinary iodine excretion (24UIE) is regarded as a more accurate indicator of iodine status compared to spot UIC, and is currently considered the gold standard for assessing iodine nutrition. When direct 24-hour urine collection is not feasible, an estimated 24UIE

(e24UIE) can be derived using an equation that incorporates spot UIC, urinary creatinine concentration, and reference values for expected 24-hour creatinine excretion based on age and sex. For best accuracy, spot urine samples used for this estimation should not be collected from the first

morning void<sup>(26)</sup>. The median e24UIE is expected to be greater than 225 µg/day, based on a recommended daily iodine intake of 250 µg, of which approximately 90% is eliminated through urine<sup>(29)</sup>. The equation proposed by Knudsen for

$$\text{e24UIE } (\mu\text{g}/24 \text{ hours}) = \frac{\text{Urinary iodine } (\mu\text{g} / \text{L})}{\text{Urinary creatinine (g/L) / Expected creatinine excretion (g/day)}}$$

Expected 24-hour creatinine excretion for women<sup>(31)</sup>

- 1.23 g for age 25-49 years old
- 1.15 g for age 50-59 years old
- 1.07 g for age 60-69 years old
- 1.00 g for age ≥ 70 years old

### **Serum iodine concentration**

After being consumed, iodate is converted into iodide within the gastrointestinal tract. Over 90% of this iodide is absorbed primarily in the stomach and duodenum. Iodide is completely bioavailable and fully absorbed into the bloodstream. Once in circulation, inorganic iodide is transported to the thyroid, where anywhere from 5% to 100% of it may be taken up, depending on the body's iodine levels<sup>(19)</sup>. Nonpregnant individuals with normal thyroid function typically have plasma iodine concentrations ranging from 40 to 80 µg /L<sup>(32)</sup>. A study conducted in Tianjin, China—an area with adequate iodine intake—found that pregnant women with serum iodine concentrations (SIC) below 79.9 µg/L had a significantly higher risk of developing hypothyroxinemia compared to those with higher SIC levels (odds ratio [OR] 2.44, 95% confidence interval [CI] 1.31–4.75). Conversely, women with SIC levels above 138.5 µg/L were more likely to experience thyrotoxicosis than those with lower SIC levels (OR 13.52, 95% CI 4.21–43.36). The median UIC observed in the study was 156 µg/L<sup>(33)</sup>. Another study carried out in Hangzhou, China—an area with iodine deficiency—reported a median serum iodine concentration (SIC) of 54.44 µg/L, with a range of 3.57 to 128.68 µg/L. In the same study, the median UIC was found to be 128.07 µg/L<sup>(34)</sup>. Additionally, a

estimating 24-hour urinary iodine excretion (e24UIE) is presented below and has demonstrated a Pearson correlation coefficient of 0.62 when compared to directly measured 24-hour urinary iodine values<sup>(30)</sup>.

study conducted in Fuzhou, China—an area with mild iodine deficiency and a median UIC of 143.4 µg/L—established a reference range for SIC in healthy pregnant women to be between 45.03 and 112.44 µg/L<sup>(35)</sup>. Further research is necessary to determine the normal reference range of serum iodine levels during pregnancy.

### **Serum thyroglobulin (Tg)**

Thyroglobulin (Tg) is a glycoprotein produced by thyrocytes and plays a crucial role in the synthesis of thyroid hormones T3 and T4<sup>(36)</sup>. Once synthesized, Tg is transported to and stored in the follicular colloid of the thyrocyte, where it undergoes iodination and coupling reactions to form T3 and T4<sup>(37, 38)</sup>.

When iodine intake is inadequate, reduced circulating T4 levels trigger the release of TRH from the hypothalamus, leading to increased secretion of TSH from the pituitary. TSH promotes the synthesis and breakdown of Tg and also stimulates the growth and proliferation of follicular cells, resulting in thyroid gland enlargement, known as goiter<sup>(39)</sup>.

In cases of iodine deficiency, elevated amounts of Tg are released into the bloodstream, with Tg levels showing a positive correlation with thyroid volume. For instance, the average Tg concentration in healthy adults ranges from 5 to 14 µg/L, while individuals with endemic goiter may have mean Tg levels between 94 and 208 µg/L<sup>(40)</sup>. Bath et al.'s study found that serum Tg levels were significantly higher in the low iodine (18 vs 16 µg/L,  $p < 0.001$ ), while there was no significant difference in TSH levels between the groups ( $p = 0.27$ )<sup>(41)</sup>. A meta-analysis revealed that the average Tg concentration in iodine-deficient

pregnant women was higher than in those with sufficient iodine levels—10.73 µg/L (95% CI: 5.65–15.82) compared to 7.34 µg/L (95% CI 2.20–12.47). However, the overlapping 95% confidence intervals indicate that the difference was not statistically significant<sup>(42)</sup>. Further research is warranted to better understand the role of thyroglobulin in assessing iodine status during pregnancy.

### **Breastmilk iodine concentration (BMIC)**

Breastfed infants depend on their mother's dietary iodine intake to meet their iodine needs. Iodine is concentrated in breast milk at levels 20–50 times higher than in plasma, due to the upregulation of the sodium-iodide symporter in lactating mammary cells<sup>(43)</sup>. Following acute iodine intake via potassium iodide (KI), peak iodine concentrations in breastmilk were observed at approximately six hours post-administration<sup>(44)</sup>. Like UIC, breastmilk iodine concentration (BMIC) shows significant intraindividual variability due to fluctuations in iodine intake, making it unsuitable as a marker of individual iodine status without multiple repeated measurements. Ideally, BMIC should be assessed using inductively coupled plasma mass spectrometry (ICP-MS) following alkali digestion for sample preparation<sup>(5)</sup>. While further globally representative studies are necessary, existing data indicate that breastmilk iodine concentrations around 150 µg/L during the first six months of lactation are likely sufficient to achieve or exceed iodine equilibrium in infants and help prevent the developmental effects of iodine deficiency<sup>(45)</sup>.

### **Other investigation methods**

Iodine deficiency leads to a decrease in circulating T4 levels and an increase in serum TSH levels. The difference in TSH levels among individuals is small, with considerable overlap, making blood TSH concentration an unreliable indicator of iodine deficiency in school-age children and adults. In

contrast, TSH levels in newborns serve as a useful indicator of iodine deficiency. Unlike adults, neonates have lower iodine stores in the thyroid, resulting in a much higher iodine turnover rate. This turnover increases even more when iodine is lacking, leading to greater TSH stimulation. As a result, newborns in iodine-deficient populations often exhibit elevated TSH levels during the first few weeks of life—a condition known as transient hyperthyrotropinemia<sup>(25)</sup>. The rise in the number of newborns with moderately elevated TSH levels (above 5 mIU/L in whole blood) corresponds to the severity of iodine deficiency during pregnancy<sup>(46)</sup>. In regions where iodine deficiency is severe, this percentage can exceed 40%. Using a sensitive TSH test on blood samples taken three to four days after birth, a population is considered iodine sufficient if fewer than 3% of newborns have TSH levels above 5 mIU/L<sup>(47)</sup>.

In cases of mild to moderate iodine deficiency disorders, palpation of thyroid gland has low sensitivity and specificity. Moreover, Thyroid size in a population may take several months or even years to return to normal after iodine deficiency has been corrected<sup>(25)</sup>. Ultrasonography offers a more accurate assessment of thyroid volume than palpation. A study conducted in Egypt observed that the thyroid volume in pregnant women was slightly higher than in non-pregnant control subjects, but the difference was not statistically significant ( $8.6 \pm 2.9$  vs  $7.9 \pm 2.5$  mL,  $p$  value = 0.126)<sup>(48)</sup>. Furthermore, research from Spain reported that in women with adequate iodine levels during the first and third trimesters, thyroid volume increased by 17.7% from baseline. In contrast, those with insufficient iodine intake experienced a much greater increase of 42.5%, highlighting the impact of iodine status on thyroid enlargement during pregnancy<sup>(49)</sup>. The distribution of thyroid volume percentiles by pregnancy trimester, along with the corresponding reference ranges, was analyzed from previous study and presented in Table 4.

**Table 4.** Thyroid volume percentiles based on the trimester of pregnancy<sup>(50)</sup>.

| Trimester | Thyroid volume (mL) according to their percentile |      |      |      |       |
|-----------|---------------------------------------------------|------|------|------|-------|
|           | 2.5                                               | 25   | 50   | 75   | 97.5  |
| First     | 2.47                                              | 4.45 | 5.28 | 6.58 | 9.49  |
| Second    | 3.17                                              | 4.41 | 5.36 | 6.58 | 9.01  |
| Third     | 3.00                                              | 4.77 | 5.55 | 6.00 | 12.38 |

**Sources of iodine**

Typical dietary sources of iodine include iodized salt, dairy products (partly due to the use of iodophor sanitizers for milk equipment, iodine-enriched cattle feed, and iodate-based bread conditioners in some breads), seaweed and other seafood, as well as drinking water<sup>(19)</sup>.

To prevent iodine deficiency, salt is commonly fortified with a controlled amount of potassium iodate (KIO<sub>3</sub>) or potassium iodide (KI), with potassium iodate being the preferred compound. The WHO recommends that iodized salt at the production stage should contain between 20 and 40 milligrams of iodine per kilogram of salt. This level of fortification is intended to supply approximately 150 micrograms of iodine per person per day. When this guideline is followed, the median urinary iodine concentration in the population is typically expected to range from 100 to 199 micrograms per liter, indicating adequate iodine intake<sup>(25)</sup>. Thailand has mandated the iodization of food-grade salt since 1994. In addition, a 2010 regulation issued by the Thai

FDA requires that fish sauce, mixed fish sauce, and seasonings produced through the hydrolysis or fermentation of soybean protein must contain between 2 and 3 milligrams of iodine per liter. As a result, the iodine intake from iodized salt used in processed foods is sufficient to meet nearly 100% of the estimated average requirement (EAR) for non-pregnant adults<sup>(51)</sup>.

Iodine levels in retail milk are not regulated by standardized guidelines, resulting in significant variability—ranging from 91 µg/L to 489 µg/kg. This variation is primarily influenced by the iodine content in the feed given to lactating animals, which has been shown to have a linear relationship with the iodine concentration in the milk<sup>(52)</sup>.

The iodine concentration in seaweeds varies significantly and is influenced by several factors, including the species, plant part, growth stage, season, and geographic origin. Typically, brown seaweeds contain higher levels of iodine compared to red or green varieties. This variation is detailed in Table 5<sup>(53)</sup>.

**Table 5.** Iodine concentration range in edible seaweed types (µg/g DW)<sup>(54-56)</sup>.

| Classification and species | Common names                                   | Iodine content (µg/g DW) | Grams of seaweed required to achieve daily iodine intake of 150 µg/ day |
|----------------------------|------------------------------------------------|--------------------------|-------------------------------------------------------------------------|
| Green algae (Chlorophyta)  | Wakame, Sea lettuce                            | 30 - 185                 | 2.0 - 6.0                                                               |
| Red algae (Rhodophyta)     | Dulse, dillisk, Nori, Irish wakame, Irish moss | 20 - 200                 | 0.3 - 3.0                                                               |
| Brown algae (Phaeophyceae) | Kombu                                          | 2,500 - 10,000           | 0.01 - 0.04                                                             |

A meta-analysis comprising seven studies from China, two from India, and one from Spain reported a broad range in median iodine concentrations in drinking water, spanning from 2.2 µg/L to 617.8 µg/L<sup>(57)</sup>. In some regions, including Djibouti, Somalia, and parts of China, water with high

iodine content can be the predominant source of dietary iodine intake<sup>(19)</sup>.

Another source of iodine for pregnant women is multivitamin supplements, which typically contain between 150 and 200 micrograms of iodine per tablet as shown below in Table 6.

**Table 6.** Iodine content in supplement tablets (µg/tablet)<sup>(58-60)</sup>.

| Commercial supplement brand | Iodine content (µg/tablet) |
|-----------------------------|----------------------------|
| Triferdine                  | 150                        |
| Nataral-EZ                  | 150                        |
| Obimin-AZ                   | 200                        |

**Impact of iodine deficiency**

***Pregnant women***

Iodine deficiency could lead to hypothyroidism and goiter. Hypothyroidism presents with a broad spectrum of symptoms, which may be asymptomatic or, in rare cases, become severe and life-threatening. Hallmark symptoms commonly include fatigue, lethargy, unexplained weight gain, and heightened sensitivity to cold<sup>(61)</sup>. Adverse cardiovascular alterations may occur in pregnant individuals, including diastolic hypertension, bradycardia, elevated serum cholesterol levels, low-output congestive heart failure, and the presence of pericardial effusion<sup>(62)</sup>.

Overt hypothyroidism during pregnancy has been linked to a higher incidence of complications such as pregnancy-induced hypertension, placental abruption, postpartum hemorrhage, preterm birth, low birthweight, and fetal death<sup>(63, 64)</sup>. Supporting this, a large U.S. national cohort study conducted in 2013, involving 223,512 pregnant women, found that untreated overt maternal hypothyroidism was significantly associated with increased risks of preeclampsia, gestational diabetes mellitus, preterm delivery, cesarean section, and admission of the newborn to a neonatal intensive care unit<sup>(65)</sup>. In contrast, the effects of maternal subclinical hypothyroidism remain less clearly defined, with conflicting findings reported across various cohort

studies. These discrepancies may stem from differences in the timing of TSH assessments, the diagnostic thresholds applied for subclinical hypothyroidism, and variability in evaluating thyroid peroxidase (TPO) antibody status. Despite these inconsistencies, accumulating evidence indicates a potential association between subclinical hypothyroidism during pregnancy and adverse outcomes, including an elevated risk of miscarriage and preterm birth<sup>(66)</sup>.

***Lactating women***

While a definitive link between iodine status and the incidence of postpartum thyroiditis has not been conclusively demonstrated, certain studies have suggested a potential association between excessive iodine intake and an increased prevalence of TPO antibody positivity, although these findings have not been uniformly replicated across all investigations<sup>(5)</sup>. Recent research involving women with pregestational Hashimoto's thyroiditis indicates that maternal thyroid function in early pregnancy may serve as a predictor for the development of postpartum thyroiditis. Interestingly, the findings suggest that euthyroid status during early gestation is associated with a greater incidence of postpartum thyroiditis compared to those who were hypothyroid. The authors proposed that the likelihood of developing postpartum thyroiditis may be influenced by the volume of remaining functional

thyroid tissue<sup>(67)</sup>.

### ***Fetus, neonate and childhood***

Thyroid hormones play a crucial role in brain development, including neurogenesis, neuronal migration, synapse formation, and myelination. A deficiency of iodine during pregnancy, particularly in the first trimester, can lead to permanent brain damage<sup>(68)</sup>.

Severe iodine deficiency, identified by a median UIC of less than 50 µg/L, is linked to negative outcomes such as stillbirth, newborn death, and impaired fetal growth<sup>(69-71)</sup>. Cretinism is the most severe consequence of iodine deficiency during pregnancy and presents in two distinct forms: neurological and myxedematous. It affects an estimated 4% to 10% of children born to mothers with severe iodine deficiency. The neurological form is more prevalent and is marked by cognitive impairment, speech and hearing problems, strabismus, difficulties with motor control, spastic movements, and ataxia<sup>(72)</sup>.

In contrast, myxedematous cretinism results from prolonged or severe hypothyroidism and is characterized by symptoms such as myxedema, stunted growth, delayed physical development, skeletal abnormalities, coarse and dry skin, thinning hair and nails, sluggish tendon reflexes, and constipation. Myxedematous cretinism is more commonly associated with postnatal hypothyroidism. Despite their distinct origins and clinical profiles, both neurological and myxedematous forms of cretinism share several overlapping neurological features. These include neurocognitive delays, hearing impairment, abnormalities in motor control due to pyramidal or extrapyramidal system dysfunction, the persistence of primitive reflexes, and other signs of central nervous system involvement. These shared features highlight the critical role of thyroid hormones not only during fetal brain development but also in the early postnatal period, emphasizing the need for both prenatal and continued postnatal monitoring and management of iodine status<sup>(73, 74)</sup>.

Mild to moderate iodine deficiency is classified by a median UIC ranging from 50 to 150 µg/L<sup>(69, 75, 76)</sup>.

Even mild to moderate maternal iodine deficiency has been associated with subtle but significant impairments in offspring's neurocognitive development, including lower intelligence quotient (IQ) scores, delayed language acquisition, reduced executive function, and poorer educational achievement<sup>(77, 78)</sup>. Findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) revealed that children born to mothers with an iodine-to-creatinine ratio below 150 µg/g were significantly more likely to have lower scores in verbal IQ, reading accuracy, and reading comprehension<sup>(79)</sup>.

The adverse outcomes identified in both maternal and neonatal health highlight the essential role of adequate iodine intake during pregnancy and lactation. Sufficient iodine status is critical not only for optimal neurodevelopment in the offspring but also for supporting normal fetal growth and minimizing the risk of obstetric complications.

## **Conclusion**

Iodine deficiency continues to represent a major global public health concern, despite being entirely preventable. Its association with increased risks of adverse maternal outcomes, impaired fetal growth, and suboptimal neurocognitive development in offspring underscores the critical importance of ensuring adequate iodine intake during pregnancy and lactation. Owing to increased demands during these periods, the WHO recommends a daily iodine intake of 250 µg for pregnant and lactating women. Although 24UIE remains the gold standard for assessing iodine status, it is often impractical in clinical and population settings. Consequently, median UIC is widely used as a reliable, population-level biomarker, with a range of 150 - 249 µg/L indicating adequacy in pregnancy. The UIC/Cr ratio has been proposed as a more robust indicator in pregnant women, as it accounts for urine dilution and inter-individual variability in hydration status. Alternative biomarkers, including serum iodine concentrations and serum thyroglobulin, require further validation to establish clinical utility and standardized reference ranges. Universal salt iodization has been instrumental in

reducing the global burden of iodine deficiency; however, continued surveillance and region-specific studies are warranted. Further research is needed to refine iodine assessment methodologies, particularly in serum and breast milk, and to evaluate iodine sufficiency across diverse populations and geographical contexts to inform future public health strategies.

## Potential conflicts of interest

The authors declare no competing interests.

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## GYNAECOLOGY

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# Biochemical and Metabolic Disruptions in Endometriosis

Deepthi Sudharma, MSc\*,  
Natrajan Muninathan, Ph.D\*\*,  
Arumugam Suresh, Ph.D\*\*\*,  
Mohanalakshmi Parthasarathy, MBBS, M.D.\*\*\*\*,  
Sheeja Mullukalayil Joseph, MSc\*,  
Bobby Joseph, MSc\*,  
Sindhu Koyilerian, MSc\*,  
Jineesh Valluvanga Chalil, MSc\*,  
Jayasudha Edatholath, MSc\*,  
Priya Raveendran, MSc\*,  
Dinesh Roy Divakaran, Ph.D\*\*\*\*\*.

\* Meenakshi Academy of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu, India

\*\* Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research (Deemed to be University), Kanchipuram, Tamil Nadu, India

\*\*\* Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research (Deemed to be University), Kanchipuram, Tamil Nadu, India

\*\*\*\* Department of Biochemistry, Sri Muthukumaran Medical College Hospital and Research, Chennai, Tamil Nadu, India

\*\*\*\*\* Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India

### ABSTRACT

**Objectives:** Endometriosis is a chronic gynecological disorder characterized by endometrial glands and stroma outside the uterine cavity. This study aimed to characterize biochemical, hormonal, and inflammatory alterations in endometriosis, with the goal of gaining insights into disease mechanisms and exploring candidate biomarkers that could inform future studies on early diagnosis or targeted interventions.

**Materials and Methods:** A case-control study enrolled 300 participants aged 20 to 45 years, including 150 individuals diagnosed with endometriosis and 150 healthy controls recruited from hospitals across Thiruvananthapuram. Serum interleukin-6 (IL-6), prolactin, luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured using enzyme linked immunosorbent assay (ELISA), while triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) were analyzed via chemiluminescent immunoassay (CLIA). Metabolic parameters were assessed using a semi-automated analyzer.

**Results:** Findings suggested that women with endometriosis had significantly higher body mass index (BMI), abdominal circumference, fasting blood sugar (FBS), triglycerides, low-density lipoprotein (LDL), IL-6, TSH, prolactin, and FSH, while high-density lipoprotein (HDL), T3, T4, and LH levels were lower ( $p < 0.05$ ). Clinical conditions such as diabetes mellitus, dyslipidemia, thyroid disorders, polycystic ovarian syndrome (PCOS), and psychological

stress were more prevalent in cases. Receiver operating characteristic analysis identified prolactin and IL-6 as the strongest diagnostic predictors, while multivariable analysis confirmed body mass index, abdominal circumference, prolactin, and IL-6 as key factors associated with endometriosis.

**Conclusion:** This study revealed key biochemical and metabolic disruptions in endometriosis, linking obesity, PCOS, and stress to disease progression, and highlighted potential biomarkers for early diagnosis and targeted treatment.

**Keywords:** endometriosis, interleukin-6, metabolic disruptions, obesity, psychological stress.

**Correspondence to:** *Natrajan Muninathan, Ph.D., Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research (Deemed to be University), Kanchipuram, Tamil Nadu, India. E-mail: muninathanpappaiya@gmail.com and Dinesh Roy Divakaran, Ph.D, Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India. Email: drdineshroyd@gmail.com*

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## Introduction

Endometriosis, a systemic proinflammatory condition affecting 5–15% of women of reproductive age worldwide, is characterized by the ectopic growth of endometrial-like tissue outside the uterus, leading to dysmenorrhea, dyspareunia, and occasionally infertility<sup>(1)</sup>. The development of endometriosis involves biochemical, endocrine, immune, and proinflammatory processes that interact with each other<sup>(2)</sup>.

Inflammation is a critical factor in the pathogenesis of endometriosis, driving cellular proliferation and tissue infiltration. Macrophages play a central role in this process, as their activation leads to the secretion of proinflammatory cytokines, which contribute to lesion progression and disease chronicity. Notably, cytokines such as interleukin (IL) (IL-6, IL-8, IL-33), nuclear factor kappa B (NF- $\kappa$ B), and tumor necrosis factor-alpha (TNF- $\alpha$ ) have been extensively studied for their involvement in various stages of endometriosis, facilitating inflammation, angiogenesis, and tissue remodeling<sup>(3)</sup>. IL-6, a pro-inflammatory cytokine, plays a significant role in the pathogenesis of endometriosis and has been suggested as a potential biomarker for its detection<sup>(4)</sup>.

Endometriosis is a hormone-dependent disorder involving endocrine dysfunction and multiple contributing factors<sup>(5)</sup>. Studies suggest a link between endometriosis and thyroid dysfunction, with an

increased risk of thyroid disease in affected individuals. Thyroid hormones may influence disease progression by modulating the immune response, activating neutrophils and macrophages, and creating a proinflammatory environment<sup>(6)</sup>. Elevated serum thyroid-stimulating hormone (TSH) or thyroxine (T4) levels have also been proposed as potential contributors to endometriosis development<sup>(7)</sup>. Key reproductive hormones follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin play crucial roles in the pathophysiology of endometriosis. Altered FSH and LH levels disrupt ovarian function, hormonal balance, and inflammation, promoting endometriosis progression, while prolactin, beyond lactation, contributes to menstrual irregularities, infertility, and cytokine-mediated inflammation. These hormones interact within the hypothalamic–pituitary–gonadal (HPG) axis, and dysregulation drives endometriosis progression<sup>(8–10)</sup>.

Apart from being a hormone-dependent and chronic disease, endometriosis also influences systemic metabolic indicators, including glucose and lipid metabolism<sup>(11)</sup>. Recent research has increasingly emphasized the connection between metabolic status and endometriosis<sup>(12)</sup>. Women with endometriosis frequently exhibit lipid profile abnormalities, such as decreased high-density lipoprotein cholesterol (HDL-C) levels and elevated triglycerides (TG), total

cholesterol (TC), and LDL levels<sup>(13)</sup>. These findings highlight a strong link between lipid metabolism disorders and endometriosis, suggesting that lipid profiles could serve as accessible indicators and potential biomarkers for the disease<sup>(14)</sup>. In addition to lipid metabolism, glucose metabolism is also implicated in endometriosis. Elevated fasting blood sugar (FBS) levels suggest a potential link between glucose dysregulation and endometriosis, with a causal association reported in recent studies<sup>(11, 15)</sup>.

The pathophysiology of endometriosis extends beyond hormonal regulation, involving immune responses and metabolic dysregulation. This study delves into these interactions, highlighting body mass index (BMI), polycystic ovary syndrome (PCOS), and psychological stress as potential contributors to disease progression and identifying biomarkers for targeted intervention.

## Materials and Methods

A case-control study aimed to investigate biochemical and metabolic disruptions associated with endometriosis. A total of 300 subjects were included, consisting of 150 endometriosis case subjects and 150 healthy controls. The participants were recruited from multiple reputed hospitals in Thiruvananthapuram like Credence Hospital, Pran Fertility and Well Woman Centre, polygenic risk score (PRS) Hospital Pvt Ltd, Yana Women's Hospital & Fertility Centre etc, in collaboration with Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, where all laboratory investigations were performed.

In this study, the case group comprised clinically confirmed endometriosis subjects. For most cases, diagnosis was confirmed through laparoscopy, with histopathological evidence of endometrial glands and stroma located outside the uterine cavity. In instances where laparoscopy was not feasible, diagnosis was made based on transvaginal ultrasound (TVUS) performed by experienced gynecologists.

The exclusion criteria for cases included chronic metabolic or endocrine disorders, such as adrenal dysfunction or other significant hormonal abnormalities.

However, women with PCOS and thyroid dysfunction (hypothyroidism or hyperthyroidism) were included, as these conditions and their associated biochemical and metabolic markers were specifically evaluated in relation to endometriosis. PCOS was diagnosed based on the Rotterdam criteria, which require two of the following: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound, with other etiologies excluded.

Controls were defined as women with no clinical signs or history of endometriosis, including absence of chronic pelvic pain, dysmenorrhea, dyspareunia, or infertility. All controls underwent a clinical pelvic examination, and TVUS was performed by qualified gynecologists to exclude ovarian endometriomas or any ultrasound findings suggestive of endometriosis. Exclusion criteria for controls also included any prior diagnosis of endometriosis, known metabolic diseases, or ongoing hormone therapy.

Data collection included demographic factors and lifestyle factors. A detailed questionnaire was given to the case subjects and the healthy controls to acquire the demographic and lifestyle factors. After obtaining informed consent, 8-10 ml of fasting venous blood was collected from the subjects. Biochemical parameters including IL-6, prolactin, LH, and FSH were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Origin Diagnostics and Research, Kerala, India), following manufacturers protocols. Thyroid hormones (T3, T4, and TSH) were analyzed via clinical laboratory improvement amendments (CLIA) using Siemens Immulite 1000, India.

Metabolic parameters, including FBS, TC, TG, HDL, and LDL were measured using enzymatic colorimetric methods on a semi-automated clinical chemistry analyzer (Mispa neo, Agappe Diagnostics Ltd., India). Psychological stress was assessed using the Perceived Stress Scale (PSS-10), a 10-item self-report questionnaire that measures perceived levels of stress over the past month. A score > 20 was considered indicative of moderate to high stress.

A robust statistical framework was applied. Data were assessed for normality using the Shapiro-Wilk

test. Depending on data distribution, comparisons between cases and controls were performed using either independent t-tests for normally distributed variables or Mann–Whitney U tests for non-normally distributed variables. Descriptive statistics summarized data using means, standard deviations, and percentages. Diagnostic potential of biochemical markers was evaluated using receiver operating characteristic (ROC) curve analysis, reporting area under the curve (AUC) values, optimal cutoffs via the Youden Index, and additional metrics like sensitivity, and specificity. Multivariable logistic regression analysis was performed to identify independent factors associated with endometriosis. Variables included in the multivariable model were selected based on clinical relevance and significant differences observed in univariate analyses ( $p < 0.05$ ). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. A  $p$  value  $< 0.05$  indicated statistical significance. Data management was performed in Microsoft Excel, and analyses were

conducted using JAMOVI version 2.5.3.

## Results

The study included 300 subjects, comprising 150 individuals with endometriosis (mean age:  $34.9 \pm 5.1$  years) and 150 controls (mean age:  $34.9 \pm 6.3$  years), all meeting the specified inclusion and exclusion criteria. The comparison of anthropometric, biochemical, and hormonal parameters between individuals with endometriosis and controls revealed significant differences in multiple variables. Cases exhibited higher abdominal circumference, weight, and BMI ( $p = 0.001$ ). Metabolic markers, including FBS, TG, TC, and LDL were significantly elevated, while HDL was lower in cases ( $p = 0.001$ ). Inflammatory marker IL-6 was markedly higher ( $p = 0.001$ ). Thyroid function tests showed lower T3 and T4 but higher TSH in cases ( $p = 0.001$ ). Reproductive hormone analysis indicated elevated FSH and prolactin levels, while LH was lower in cases ( $p < 0.05$ , t-test) (Table 1).

**Table 1.** Comparison of anthropometric, biochemical, and hormonal parameters between individuals with endometriosis and controls.

| Parameter                                  | Control Group<br>(n = 150)<br>Mean $\pm$ SD | Case Group<br>(n = 150)<br>Mean $\pm$ SD | t-value | p value |
|--------------------------------------------|---------------------------------------------|------------------------------------------|---------|---------|
| Age (years)                                | 34.9 $\pm$ 6.3                              | 34.9 $\pm$ 5.1                           | 0.081   | 0.936   |
| Abdominal Circumference (cm)               | 85.0 $\pm$ 12.6                             | 95.9 $\pm$ 11.7                          | 7.744   | < 0.001 |
| Height (cm)                                | 155.6 $\pm$ 6.1                             | 155.6 $\pm$ 6.1                          | 2.140   | 0.033   |
| Weight (kg)                                | 57.2 $\pm$ 9.2                              | 64.0 $\pm$ 10.6                          | 5.961   | < 0.001 |
| BMI (kg/m <sup>2</sup> )                   | 23.6 $\pm$ 3.3                              | 27.0 $\pm$ 4.2                           | 7.860   | < 0.001 |
| Fasting blood sugar (FBS) (mg/dL)          | 89.5 $\pm$ 13.4                             | 122.5 $\pm$ 42.7                         | 9.035   | < 0.001 |
| Triglycerides (TG) (mg/dL)                 | 117.3 $\pm$ 22.2                            | 159.9 $\pm$ 39.3                         | 11.547  | < 0.001 |
| Total cholesterol (TC) (mg/dL)             | 174.0 $\pm$ 32.5                            | 231.5 $\pm$ 42.3                         | 13.211  | < 0.001 |
| High-density lipoprotein (HDL) (mg/dL)     | 49.8 $\pm$ 6.7                              | 42.8 $\pm$ 6.6                           | 9.137   | < 0.001 |
| Low-density lipoprotein (LDL) (mg/dL)      | 100.8 $\pm$ 31.8                            | 156.8 $\pm$ 36.8                         | 14.109  | < 0.001 |
| Interleukin-6 (IL-6) (pg/mL)               | 3.18 $\pm$ 1.99                             | 7.74 $\pm$ 5.13                          | 10.152  | < 0.001 |
| Triiodothyronine (T3) (ng/dL)              | 118.6 $\pm$ 19.5                            | 78.2 $\pm$ 21.9                          | 16.890  | < 0.001 |
| Thyroxine (T4) (ng/dL)                     | 7.73 $\pm$ 1.77                             | 6.17 $\pm$ 2.44                          | 6.340   | < 0.001 |
| Thyroid-stimulating hormone (TSH) (mIU/L)  | 2.40 $\pm$ 1.07                             | 6.66 $\pm$ 4.04                          | 12.512  | < 0.001 |
| Follicle-stimulating hormone (FSH) (mIU/L) | 14.1 $\pm$ 5.7                              | 15.9 $\pm$ 5.5                           | 2.921   | 0.004   |
| Luteinizing hormone (LH) (mIU/L)           | 13.9 $\pm$ 3.7                              | 12.0 $\pm$ 5.8                           | 3.339   | < 0.001 |
| Prolactin (ng/mL)                          | 13.2 $\pm$ 5.4                              | 27.3 $\pm$ 9.5                           | 15.773  | < 0.001 |

The study revealed significant differences in the prevalence of various clinical conditions between the control and case groups (Table 2). Diabetes was more prevalent in the case group (16.7%) compared to the control group (3.3%) with a statistically significant difference ( $\chi^2 = 14.8$ ,  $p = 0.001$ ). Similarly, dyslipidemia was more common in the case group (17.3%) compared to the control group (6%) ( $\chi^2 = 9.35$ ,  $p = 0.002$ ). A significantly higher incidence of

thyroid disorders was observed in the case group (23.3%) compared to the control group (4.7%) ( $\chi^2 = 21.7$ ,  $p = 0.001$ ). Psychological stress was more prevalent in the case group (18.7%) than in the control group (8.7%) ( $\chi^2 = 6.36$ ,  $p = 0.012$ ). Additionally, the prevalence of PCOS was higher in the case group (18%) compared to the control group (7.3%) ( $\chi^2 = 7.71$ ,  $p = 0.005$ ). All differences were statistically significant, with  $p$  values less than 0.05.

**Table 2.** Association of various clinical variables between the case and control group.

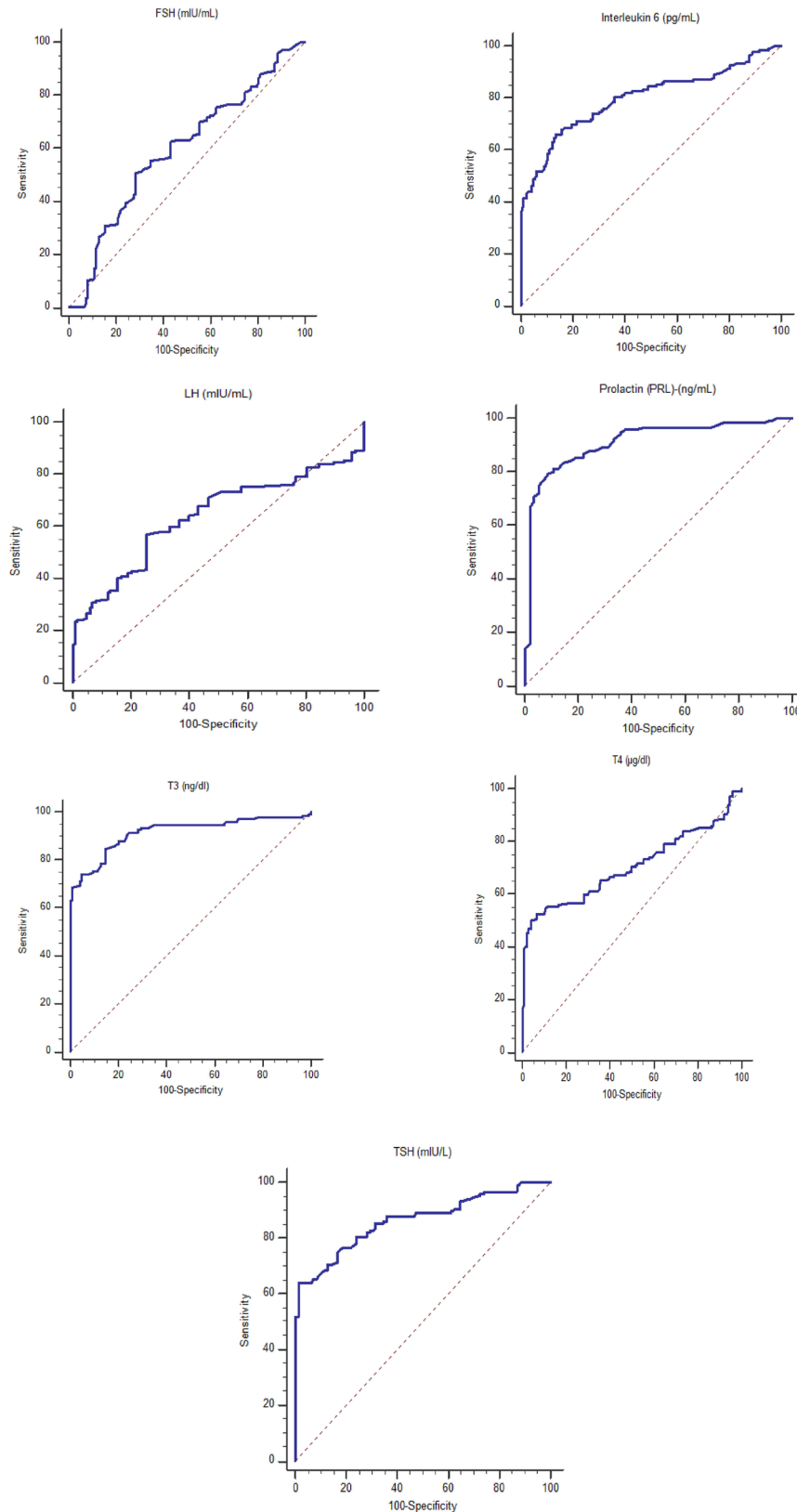
| Comorbidity          | Group   | n (%)      | $\chi^2$ | df | p value |
|----------------------|---------|------------|----------|----|---------|
| Diabetes             | Control | 5 (3.3%)   | 14.8     | 1  | 0.001   |
|                      | Case    | 25 (16.7%) |          |    |         |
| Dyslipidemia         | Control | 9 (6.0%)   | 9.35     | 1  | 0.002   |
|                      | Case    | 26 (17.3%) |          |    |         |
| Thyroid Disorder     | Control | 7 (4.7%)   | 21.7     | 1  | 0.001   |
|                      | Case    | 35 (23.3%) |          |    |         |
| Psychological Stress | Control | 13 (8.7%)  | 6.36     | 1  | 0.012   |
|                      | Case    | 28 (18.7%) |          |    |         |
| PCOS                 | Control | 11 (7.3%)  | 7.71     | 1  | 0.005   |
|                      | Case    | 27 (18.0%) |          |    |         |

PCOS: polycystic ovarian syndrome

The ROC curve demonstrates the diagnostic ability of the test, with the AUC indicating its overall accuracy. A higher AUC value suggests better test performance, with values closer to 1.0 representing excellent diagnostic ability (Fig. 1). Prolactin demonstrated the highest diagnostic performance with a significantly high AUC, making it the most reliable predictor for distinguishing between cases and controls. IL-6 was identified as a strong predictor, showing a bowed ROC curve towards the top-left corner, indicating excellent diagnostic accuracy. TSH also performed well, exhibiting a high AUC, suggesting it is a good predictor, though not as exceptional as Prolactin. T3 and FSH demonstrated moderate diagnostic performance, with AUC values above 0.5, indicating results better than random chance. In contrast, LH and T4 showed moderate diagnostic accuracy, with their

ROC curves positioned above the diagonal but not exhibiting the same level of precision as the strongest predictors.

In this study, several factors were associated with the case group (Table 3). Diabetes, dyslipidemia, thyroid disorder, and PCOS showed significant associations in the univariable analysis, but many lost significances in the multivariable analysis. Abdominal circumference ( $\geq 88$  cm) and BMI ( $\geq 25$  kg/m<sup>2</sup>) were strongly associated with the case group, with both univariable and multivariable analyses showing significant results. High levels of LH, FSH, prolactin, and IL-6 were also significantly associated with the case group, with prolactin and IL-6 showing strong associations in both analyses. Other variables, including lipid parameters and thyroid hormones, did not remain significant after adjustment.



**Fig. 1.** Receiver operating characteristic curve of various parameters

**Table 3.** Association of demographic, biochemical, and hormonal factors with case group in univariable and multivariable analyses.

| Parameter               | Control Group<br>(n = 150)<br>Mean ± SD | Case Group<br>(n = 150)<br>Mean ± SD | t-value    | p value | OR<br>(univariable)            | OR<br>(multivariable)             |
|-------------------------|-----------------------------------------|--------------------------------------|------------|---------|--------------------------------|-----------------------------------|
| Diabetes                | No                                      | 145 (96.7)                           | 125 (83.3) | < 0.001 | Ref                            | Ref                               |
|                         | Yes                                     | 5 (3.3)                              | 25 (16.7)  |         | 5.80 (2.33-17.59, p < 0.001)   | 0.33 (0.02-5.09, p = 0.416)       |
| Dyslipidemia            | No                                      | 141 (94.0)                           | 124 (82.7) | 0.004   | Ref                            | Ref                               |
|                         | Yes                                     | 9 (6.0)                              | 26 (17.3)  |         | 3.28 (1.53-7.67, p = 0.003)    | 2.38 (0.23-23.46, p = 0.448)      |
| Thyroid Disorder        | No                                      | 143 (95.3)                           | 115 (76.7) | < 0.001 | Ref                            | Ref                               |
|                         | Yes                                     | 7 (4.7)                              | 35 (23.3)  |         | 6.22 (2.82-15.74, p < 0.001)   | 7.59 (0.67-124.60, p = 0.123)     |
| PCOS                    | No                                      | 139 (92.7)                           | 123 (82.0) | 0.009   | Ref                            | Ref                               |
|                         | Yes                                     | 11 (7.3)                             | 27 (18.0)  |         | 2.77 (1.35-6.05, p = 0.007)    | 1.37 (0.19-10.59, p = 0.755)      |
| Abdominal circumference | < 88 cm                                 | 100 (66.7)                           | 29 (19.3)  | < 0.001 | Ref                            | Ref                               |
|                         | ≥ 88 cm                                 | 50 (33.3)                            | 121 (80.7) |         | 8.34 (4.98-14.35, p < 0.001)   | 17.14 (3.80-107.99, p = 0.001)    |
| BMI                     | < 25                                    | 107 (71.3)                           | 52 (34.7)  | < 0.001 | Ref                            | Ref                               |
|                         | ≥ 25                                    | 43 (28.7)                            | 98 (65.3)  |         | 4.69 (2.90-7.70, p < 0.001)    | 16.59 (2.81-167.11, p = 0.006)    |
| LH                      | > 12.25 (mIU/mL)                        | 112 (74.7)                           | 65 (43.3)  | < 0.001 | Ref                            | Ref                               |
|                         | ≤ 12.25 (mIU/mL)                        | 38 (25.3)                            | 85 (56.7)  |         | 3.85 (2.38-6.34, p < 0.001)    | 1.64 (0.41-6.81, p = 0.484)       |
| FSH                     | ≤ 15.86 (mIU/mL)                        | 108 (72.0)                           | 74 (49.3)  | < 0.001 | Ref                            | Ref                               |
|                         | > 15.86 (mIU/mL)                        | 42 (28.0)                            | 76 (50.7)  |         | 2.64 (1.64-4.29, p < 0.001)    | 1.71 (0.37-8.11, p = 0.489)       |
| Prolactin               | ≤ 18.2 (ng/mL)                          | 134 (89.3)                           | 28 (18.7)  | < 0.001 | Ref                            | Ref                               |
|                         | > 18.2 (ng/mL)                          | 16 (10.7)                            | 122 (81.3) |         | 36.49 (19.34-72.92, p < 0.001) | 124.16 (21.51-1346.30, p < 0.001) |
| IL-6                    | ≤ 5.57 (pg/mL)                          | 130 (86.7)                           | 51 (34.0)  | < 0.001 | Ref                            | Ref                               |
|                         | > 5.57 (pg/mL)                          | 20 (13.3)                            | 99 (66.0)  |         | 12.62 (7.20-23.02, p < 0.001)  | 7.91 (1.30-62.44, p = 0.032)      |

OR: odds ratio, PCOS: polycystic ovarian syndrome, BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone, IL: interleukin

## Discussion

Endometriosis cases exhibited higher BMI, abdominal circumference, and metabolic disturbances, including elevated FBS, TG, and LDL, with lower HDL (p = 0.001). IL-6, prolactin, and FSH were significantly higher, while LH was lower. Diabetes, dyslipidemia, thyroid disorders, stress, and PCOS were more prevalent in cases. Prolactin was the strongest predictor, followed by IL-6 and TSH.

Malvezzi et al emphasized the multifactorial nature of endometriosis and the challenges in modeling its pathology due to the lack of reliable animal models. They highlighted the need for novel research approaches, including artificial intelligence, three-dimensional cultures, and organ-on-chip models, to enhance understanding and improve treatment strategies. Their work focused on advancing

experimental models to study endometriosis and assess drug efficacy<sup>(16)</sup>.

In contrast, the present study directly investigated the metabolic, hormonal, and inflammatory alterations associated with endometriosis, providing clinical insights that bridge gaps in understanding disease pathophysiology. This study identified significant metabolic imbalances, including elevated FBS, TG, LDL, and reduced HDL (Table 1). Additionally, the findings highlighted the role of adiposity through increased BMI and abdominal circumference. Notably, prolactin emerged as the most potent diagnostic marker, followed by IL-6, reinforcing the inflammatory component of endometriosis (Fig. 1). Furthermore, the study established a link between thyroid dysfunction (elevated TSH, reduced T3 and T4) and endometriosis, along with a higher prevalence of

PCOS, suggesting overlapping endocrine and metabolic mechanisms.

By focusing on clinically measurable metabolic, hormonal, and inflammatory parameters, the present study addressed a critical gap left by previous researchers who primarily focused on experimental modeling rather than direct clinical and biochemical associations. These findings provided valuable diagnostic and pathophysiological insights, emphasizing the need for an integrated approach to managing endometriosis beyond current experimental models<sup>(16)</sup>.

Just like any other study, the present study had its limitations. Selection bias may exist due to hospital-based recruitment, limiting generalizability. Self-reported demographic and lifestyle data introduced the risk of recall bias. While key biochemical markers were analyzed, other relevant inflammatory markers were not included. Variability in diagnosis, with some cases relying on imaging rather than laparoscopy, may affect consistency. Despite a robust sample size, more extensive multi-center studies are needed for broader validation. Another limitation of this study was that although hormonal assays were performed, the timing of blood sampling during the menstrual cycle was not uniformly standardized across all participants. As levels of FSH and LH fluctuate significantly throughout the menstrual cycle, this may have contributed to variability and potentially higher observed values in both cases and controls. Finally, this case-control study was the potential presence of confounding factors influencing biochemical and hormonal measurements. Although multivariable analysis was performed to adjust for key confounders, residual confounding cannot be entirely excluded.

The most notable findings of the present study were the significant metabolic, hormonal, and inflammatory alterations observed in individuals with endometriosis. Cases exhibited elevated FBS, TG, and LDL levels, along with reduced HDL, indicating a metabolic imbalance (Table 1). Higher BMI and abdominal circumference further reinforced the role of adiposity in disease pathology. Notably, prolactin

demonstrated the highest diagnostic accuracy, followed by IL-6, highlighting the inflammatory component of endometriosis (Fig. 1). Thyroid dysfunction, characterized by elevated TSH and reduced T3 and T4 levels, was significantly associated with endometriosis, suggesting an endocrine-metabolic link. Additionally, the increased prevalence of PCOS in cases indicated shared pathophysiological mechanisms between the two conditions.

These findings aligned with previous research indicating an unfavorable lipid profile in women with endometriosis. One study reported higher LDL, non-HDL, TG, and TC levels, along with a lower HDL:TC ratio, in the endometriosis group compared to controls<sup>(17)</sup>. Similarly, other studies identified a link between elevated serum TG and an increased risk of endometriosis, as well as significantly lower HDL-C and higher LDL-C levels in affected individuals<sup>(18,19)</sup>. These findings suggested that metabolic dysregulation may play a crucial role in the pathophysiology of endometriosis, potentially contributing to disease progression through mechanisms involving inflammation and hormonal imbalances.

Another key metabolic alteration observed in the present study was the elevation of FBS levels in individuals with endometriosis, indicating a potential link between glucose metabolism and disease pathology (Table 1). These findings aligned with previous research that reported a significantly higher triglyceride-glucose (TyG) index in women with endometriosis compared to those without the condition, reinforcing the association between insulin resistance and endometriosis<sup>(20)</sup>. Furthermore, earlier studies supported significant causal associations between type 1 diabetes mellitus (T1DM), gestational diabetes mellitus (GDM), and fasting insulin (FI) levels in relation to endometriosis<sup>(15)</sup>. Endometriosis patients demonstrated elevated insulin (INS) levels [6.90 (5.10–9.50) vs. 6.50 (4.80–8.90)  $\mu$ U/mL,  $p = 0.005$ ], further indicating a state of insulin resistance<sup>(11)</sup>. These observations suggested that metabolic dysfunction, particularly alterations in glucose homeostasis, played a crucial role in the pathophysiology of endometriosis.

The present study supports previous research that has reported elevated IL-6 levels in individuals with endometriosis, reinforcing its role in disease pathology<sup>(21,22)</sup>. In addition to confirming these findings, the current study identified IL-6 as one of the strongest diagnostic markers, with significant associations observed in univariable and multivariable analyses (Table 3, Fig. 1). This highlights the clinical relevance of IL-6 in endometriosis and suggests its potential utility as a biomarker for disease diagnosis and progression assessment.

The present study identified prolactin as the most potent diagnostic marker for endometriosis, as shown in Fig. 1. This finding was consistent with previous research that has reported elevated serum prolactin levels in individuals with endometriosis<sup>(23)</sup>. Moreover, earlier studies have demonstrated the diagnostic utility of prolactin when assessed alongside CA-125. For instance, one study found that combining serum CA-125 (cut-off: 19.9 U/L) and prolactin (cut-off: 14.8 ng/ml) enabled the diagnosis of peritoneal endometriosis with 77% sensitivity, 88% specificity, and a high negative predictive value of 97%<sup>(24)</sup>. However, it is important to note that the current study did not evaluate other potential causes of hyperprolactinemia, such as pituitary adenomas or the use of medications that influence prolactin levels. As such, the interpretation of prolactin as a diagnostic marker should be made with caution, and further studies are needed to validate these findings while controlling for these confounding variables.

The present study identified significant hormonal alterations in individuals with endometriosis compared to controls. Elevated FSH levels and reduced LH levels were observed in the case group, suggesting disruptions in ovarian function. Additionally, thyroid dysfunction was more prevalent among cases, characterized by lower T3 and T4 levels and elevated TSH levels (Table 1). These findings indicated a potential link between hormonal dysregulation and endometriosis pathophysiology. Previous studies have reported similar patterns of hormonal imbalance in endometriosis. One study

found significantly higher FSH levels in individuals with endometriosis than controls, supporting the current study's findings<sup>(25)</sup>. Another reported decreased LH levels in affected individuals, consistent with the present results<sup>(26)</sup>. Regarding thyroid dysfunction, one group highlighted upregulated TSH receptors in ectopic endometrial tissue and elevated TRAb IgG levels in endometriosis patients, suggesting an overlap in pathophysiology<sup>(7)</sup>. Additionally, a higher prevalence of hypothyroidism was observed in women with endometriosis (9.6% vs 1.5%,  $p < 0.0001$ ), reinforcing the association between thyroid dysfunction and endometriosis<sup>(27)</sup>. These comparisons suggest that hormonal alterations may be critical in the disease's development and progression, warranting further investigation into their clinical implications.

In the present study, individuals with endometriosis exhibited higher BMI and abdominal circumference, as outlined in Table 1. Existing research suggests a correlation between BMI and endometriosis. For example, one study reported a significant association between elevated BMI and endometriosis<sup>(28)</sup>. Similarly, another study observed a higher incidence of endometriosis in obese women ( $\text{BMI} > 27.50 \text{ kg/m}^2$ ) compared to those with normal weight<sup>(29)</sup>. These findings align with the present study, reinforcing the association between increased BMI and endometriosis.

PCOS was significantly associated with endometriosis in the current study (Table 2, Table 3), aligning with previous research that supports this link. A case-control study reported a significant association between endometriosis and PCOS in women presenting with pelvic pain and/or infertility<sup>(30)</sup>. Additionally, recent findings highlighted a genetic correlation and shared risk genes between these conditions, further reinforcing the potential interplay of genetic factors in their coexistence<sup>(31)</sup>.

The significantly higher prevalence of psychological stress in the case group (18.7%) compared to the control group (8.7%) ( $\chi^2 = 6.36$ ,  $p = 0.012$ ) indicated a strong association between

endometriosis and increased stress levels, as shown in Table 2. This finding suggests that individuals with endometriosis may experience elevated stress due to factors such as chronic pelvic pain, infertility concerns, and the overall burden of managing a chronic condition. Psychological stress has been recognized as a contributing factor in the progression and symptom severity of endometriosis, potentially exacerbating inflammatory responses and pain perception. Clinical studies have consistently demonstrated that endometriosis is associated with high levels of chronic stress, reinforcing the need for a multidisciplinary approach to management that includes psychological support alongside conventional medical and surgical treatments<sup>(32, 33)</sup>.

This study underscored the multifactorial nature of endometriosis, revealing significant metabolic, hormonal, and inflammatory alterations in affected individuals. Identifying prolactin as the most potent predictive marker and IL-6 and thyroid dysfunction expands the diagnostic landscape for endometriosis. The findings emphasized the association between metabolic dysregulation and endometriosis, reinforcing the need for a comprehensive, interdisciplinary approach to disease management. Additionally, the observed overlap with PCOS and increased psychological stress further supports a shared pathophysiological basis among endocrine disorders.

Unlike prior research focused on infertility and pelvic pain, it expands the scope by linking endometriosis to metabolic syndrome, psychological stress, and endocrine dysfunction. Strengthening the case for prolactin and IL-6 as diagnostic biomarkers beyond CA-125, the findings advocate for a multidisciplinary approach. Given the limitations of hospital-based recruitment and the need for broader validation, future multi-center studies with a larger sample size should further explore the identified metabolic, endocrine, and inflammatory associations. These findings contributed to a better understanding of the systemic nature of endometriosis, paving the way for more targeted diagnostic and therapeutic

strategies beyond traditional gynecological approaches.

## Conclusion

Endometriosis is a multifaceted disorder involving chronic inflammation, hormonal imbalances, and metabolic dysfunction. This study reinforces the systemic nature of the disease by demonstrating key associations between endocrine disturbances, proinflammatory markers, and metabolic alterations. Notably, prolactin and IL-6 emerged as potential diagnostic indicators, highlighting their clinical utility. The observed interplay between immune, metabolic, and endocrine pathways underscores the importance of an integrated, multidisciplinary approach for effective diagnosis and management. Future large-scale, multi-center studies are essential to validate these findings and guide personalized therapeutic strategies.

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## Authors contribution

D.S.: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, writing – original draft;

N.M.: conceptualization, methodology, resources, supervision, writing – review & editing;

D.R.D.: conceptualization, project administration, supervision, writing – review & editing;

B.J.: data curation, investigation;

J.V.C.: data curation, investigation;

S.M.J.: data curation, investigation;

S.K.: data curation, investigation;

P.R.: data curation, investigation;

A.S.: methodology, validation;

P.M.L.: validation.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

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# Diagnostic Performance of the International Ovarian Tumor Analysis Simple Rules with CA125 in Differentiating between Benign and Malignant Adnexal Masses

Kamonlak Limsawan, M.D.\*,  
Prasong Tanmahasamut, M.D.\*,  
Vitcha Poonyakanok, M.D.\*

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

### ABSTRACT

**Objectives:** To evaluate the diagnostic performance of the International Ovarian Tumor Analysis (IOTA) simple rules in combination with serum tumor marker Cancer Antigen 125 (CA125).

**Materials and Methods:** This secondary analysis was based on a previous prospective diagnostic single-center study conducted at Siriraj Hospital, Thailand, between May 1, 2018, and May 31, 2019. Gynecological patients scheduled for an elective adnexal surgery at Siriraj Hospital were recruited. Preoperative ultrasound was performed within 120 days before surgery. The assessment included IOTA simple rules, IOTA simple rules with subjective assessment, and IOTA simple rules with CA125. The sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver operating characteristic curve (AUC) were assessed.

**Results:** A total of 357 patients from the original study cohort were included, and all were found eligible. The IOTA simple rules were applicable in 316 cases (88.5%), and achieved an AUC of 0.938 (95% CI 0.897-0.979). The IOTA simple rules along with subjective assessment demonstrated a similar AUC, 0.933 (95% CI 0.892-0.975). Integrating CA125 with the IOTA simple rules reduced the AUC to 0.825 (95% CI 0.776–0.875). When CA125 was applied exclusively to the inconclusive group, the AUC was 0.909 (95% CI 0.866–0.953). The optimal cutoff value of CA125 calculated from our cohort was 115 U/ml.

**Conclusion:** The IOTA simple rules are an excellent model for differentiating benign and malignant adnexal masses. Selective use of CA125 or subjective assessment in inconclusive cases can support decision-making.

**Keywords:** adnexal diseases, ovarian neoplasms, international ovarian tumor analysis (IOTA), simple rules, CA125

**Correspondence to:** *Prasong Tanmahasamut, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.  
E-mail: prasong.tan@mahidol.ac.th*

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# การศึกษาประสิทธิภาพในการวินิจฉัยแยกแยะก้อนที่ปีกมดลูกชนิดไม่ร้ายแรงและมะเร็งของเกณฑ์การวิเคราะห์ IOTA Simple Rules ร่วมกับการตรวจค่า CA125

กมลลักษณ์ ลิ้มสุวรรณ, ประสงค์ ตันมหาสมุทร, วิชา บุญยกรณ

## บทคัดย่อ

**วัตถุประสงค์:** เพื่อประเมินประสิทธิภาพของ International Ovarian Tumor Analysis (IOTA) simple rules เมื่อใช้ร่วมกับสารบ่งชี้มะเร็ง Cancer antigen 125 (CA125)

**วัสดุและวิธีการ:** การวิจัยนี้เป็นการวิเคราะห์หัตถิยภูมิจากการศึกษาแบบไปข้างหน้าเดิมที่จัดทำขึ้นที่โรงพยาบาลศิริราชระหว่างวันที่ 1 พฤษภาคม 2561 ถึงวันที่ 31 พฤษภาคม 2562 ผู้ป่วยนรีเวชที่มีกำหนดการเข้ารับการผ่าตัดสำหรับรังไข่และท่อนำไข่จะถูกคัดเลือกเข้าร่วมการศึกษา โดยผู้ป่วยจะได้รับการตรวจอัลตราซาวนด์ภายในเวลาไม่เกิน 120 วันก่อนการผ่าตัด การประเมินประกอบด้วย IOTA simple rules, IOTA simple rules ร่วมกับ subjective assessment และ IOTA simple rules ร่วมกับ CA125 ได้มีการประเมินค่าความไว (sensitivity) ความจำเพาะ (specificity) ค่าทำนายผลบวก (positive predictive value) ค่าทำนายผลลบ (negative predictive value) การวิเคราะห์เส้นโค้ง (Receiver operating characteristic - ROC) และ พื้นที่ใต้เส้นโค้ง (area under the curve - AUC)

**ผลการศึกษา:** ผู้ป่วยทั้งหมดจากศึกษาเดิมจำนวน 357 คนเข้าเกณฑ์การศึกษา โดยไม่มีการคัดออก เครื่องมือ IOTA simple rules สามารถใช้ได้กับผู้ป่วย 316 ราย คิดเป็น 88.5% และมีค่า AUC เท่ากับ 0.938 (95% CI 0.897–0.979) และ IOTA simple rules ร่วมกับการประเมินแบบ subjective assessment ให้ค่า AUC เท่ากับ 0.933 (95% CI 0.892–0.975) ซึ่งใกล้เคียงกัน เครื่องมือ IOTA simple rules ที่ใช้ร่วมกับ CA125 ทำให้ค่า AUC เท่ากับ 0.825 (95% CI 0.776–0.875) และเมื่อใช้ CA125 เฉพาะกับกลุ่มที่ไม่สามารถสรุปผลได้ (inconclusive group) ค่า AUC เท่ากับ 0.909 (95% CI 0.866–0.953) ค่าจุดตัด CA125 ที่เหมาะสม ที่คำนวณได้จากกลุ่มตัวอย่างคือ 115 U/ml

**สรุป:** IOTA simple rules มีประสิทธิภาพที่ดีในการจำแนกระหว่างก้อนรังไข่และปีกมดลูกที่เป็นมะเร็งและไม่เป็นมะเร็ง การใช้ CA125 หรือการประเมินแบบ subjective assessment ในกรณีที่ผลไม่สามารถสรุปได้ (inconclusive) สามารถเข้ามาช่วยในการตัดสินใจวางแผนการรักษาผู้ป่วยได้

**คำสำคัญ:** โรคของปีกมดลูก, เนื้องอกรังไข่, International Ovarian Tumor Analysis (IOTA), Simple Rules, สารบ่งชี้มะเร็ง CA125

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## Introduction

Ovarian cancer is one of the most common gynecological cancers globally<sup>(1)</sup>. In 2020, the Global Health Research Group of Association of Pacific Rim Universities reported that 207,252 women died from ovarian cancer, with increasing incidence in lower-income countries<sup>(2)</sup>. A systematic review, published in August 2015, demonstrated that patients with advanced ovarian cancer particularly benefit from medical care provided by subspecialist gynecologic oncologists. Surgery performed by subspecialist gynecologic oncologists was associated with higher survival rates, reduced need for repeat surgery, and more frequent lymphadenectomy procedures compared with surgeries performed by non-subspecialists<sup>(3)</sup>. Similarly, a study conducted in the Netherlands found that subspecialist-performed surgery was associated with higher 5-year survival rates in patients with epithelial ovarian cancer<sup>(4)</sup>.

Conversely, unnecessary surgery leading to early surgical menopause can have detrimental long-term effects, including increased long-term cardiovascular and metabolic complications, lower bone mass, and altered sexual function and sexual desire<sup>(5, 6)</sup>. Therefore, accurately distinguishing between benign and malignant adnexal masses is crucial. Various scoring systems and screening tools have been developed to distinguish between benign and malignant adnexal tumors using characteristics and biomarkers, including the Risk of Malignancy Index (RMI), International Ovarian Tumor Analysis Simple Rules (IOTA SR), Cancer antigen 125 (CA125), Human Epididymis protein 4 (HE4), Ovarian-Adnexal Reporting and Data System (O-RADS), and the Assessment of Different Neoplasias in the adnexa (ADNEX).

The International Ovarian Tumor Analysis (IOTA) group introduced the simple rules in 2008,

which rely exclusively on ultrasonographic features to support clinical decision-making. These rules consist of five benign and five malignant ultrasonographic features<sup>(7)</sup>. The IOTA SR showed high diagnostic accuracy in previous study<sup>(8)</sup> and were significantly better than RMI-2<sup>(9)</sup>. The authors believe that the IOTA SR offers a straightforward, effective, and practical approach, suitable even for non-expert ultrasonographers.

CA125 is one of the most widely utilized biomarkers for epithelial ovarian cancer, particularly in non-mucinous histological subtypes. However, its role in screening is limited due to poor sensitivity for early-stage disease<sup>(10)</sup>. Despite this limitation, CA125 remains valuable for assessing suspected malignancies and borderline tumors. Elevated CA125 levels may also be seen in several benign conditions, such as leiomyoma, pregnancy, endometriosis, and pelvic inflammatory disease<sup>(11)</sup>. To address this limitation, HE4 has been developed as a complementary biomarker with higher specificity for ovarian cancer. However, due to its higher cost and limited availability, HE4 has not replaced CA125 as the primary biomarker in routine clinical practice<sup>(12, 13)</sup>.

Although numerous studies have investigated the most effective methods for distinguishing benign from malignant adnexal lesions, the optimal diagnostic approach remains a subject of debate<sup>(14-16)</sup>. Early and accurate detection is essential to guide appropriate management, minimize complications and avoid unnecessary surgical interventions. While the IOTA SR is a straightforward and effective diagnostic tool, its limitation lies in cases with inconclusive results. To overcome this limitation without compromising simplicity, the present study aimed to assess the diagnostic performance of IOTA SR in combination with CA125 for preoperative differentiation between benign and malignant ovarian tumors.

## Materials and Methods

This was a secondary analysis of a previous prospective diagnostic study performed at the Gynecologic Ultrasonography Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. The study was performed at a single tertiary care hospital between May 1, 2018, and May 31, 2019<sup>(17)</sup>. Ethical approval was obtained from the Institutional Review Board of Siriraj Hospital (Protocol No.161/2567(IRB3), CoA no. Si 275/2024).

Patients presenting at Siriraj Hospital with adnexal masses scheduled for surgical intervention, who underwent ultrasound evaluation within 120 days prior to surgery, were recruited. None of the patients had a diagnosis of the adnexal mass through laparoscopy or previous surgery. Transvaginal ultrasonography was the primary technique used, while transabdominal ultrasonography was performed in selected cases when transvaginal ultrasonography was inadequate (GE Voluson E6 BT13.5, Milwaukee, WI, USA, equipped with 3.5-MHz and 8.0-MHz transducers). If more than one lesion was identified, the most complex lesion was included in the study. No patients were excluded from the original dataset.

The prevalence of ovarian cancer at Siriraj Hospital was 17%<sup>(17)</sup>. Drawing on pilot data from our previous prospective study<sup>(17)</sup>, the sensitivity and specificity of the IOTA SR combined with CA125 were 85.71% and 63.64%, respectively. Applying diagnostic accuracy formulas, the minimum required sample size was determined to be 48 for malignant and 277 for benign adnexal masses. Accounting for a 10% allowance for incomplete records, a total of 308 subjects was required. Consequently, the 357 participants recruited in our previous study provided sufficient data for this secondary analysis. A flow

diagram of patient recruitment and exclusion is provided in Fig. 1.

Unadjusted sample size:

Sensitivity:  $NSe(unadj) =$

$$[(Z\alpha/2)^2 Se(1 - Se)]/d^2$$

Specificity:  $NSp(unadj) =$

$$[(Z\alpha/2)^2 Sp(1 - Sp)]/d^2$$

Adjusted sample size: Sensitivity:  $NSe(prev adj) = NSe(unadj)/P$

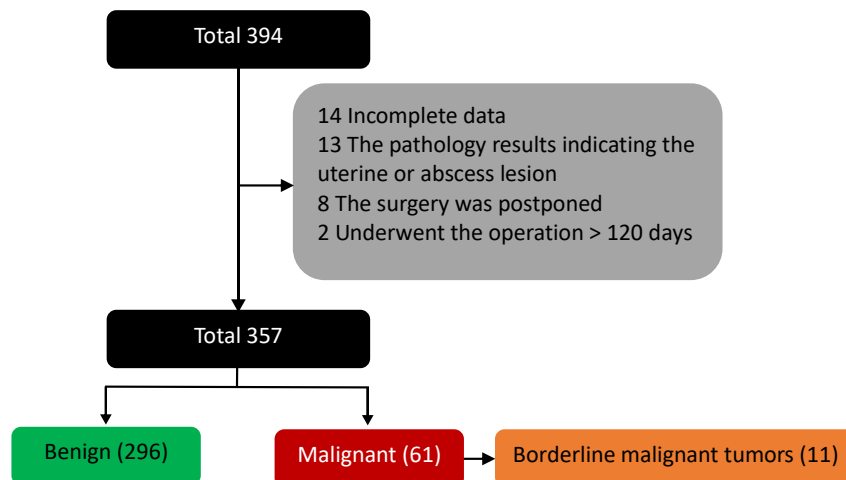
Specificity:  $NSp(prev adj) = NSp(unadj)/(1-P)$

$\alpha = 0.05$ ,  $Z(0.975) = 1.96$ ,  $p = \text{prevalence} = 0.8571$ ,  $d = \text{margin of error} = 0.10$

$Se(unadj)$ , unadjusted sensitivity;  $Sp(unadj)$ , unadjusted specificity;

$Se(prev.adj)$ , prevalence-adjusted sensitivity;  $Sp(prev.adj)$ , prevalence-adjusted specificity

Case record forms were reviewed for demographic and clinical data, including age, menopausal status, parity, and underlying diseases, with all identifiers removed. Ultrasonographic features were assessed and categorized using IOTA SR, which is a classification system used for the preoperative diagnosis of ovarian cancer<sup>(9)</sup>. According to these rules, adnexal masses are categorized as benign, malignant, or inconclusive based on the presence of benign features (B-features) or malignant features (M-features), shown in Table 1. A mass was classified as benign if one or more B-features were present in the absence of M-features. Conversely, it was classified as malignant if one or more M-features were present without any B-features. If both B-features and M-features were present, or if neither feature applied, the mass was deemed inconclusive.



**Fig. 1.** Flow diagram of the patient recruitment and exclusion.

**Table 1.** Features of the international ovarian tumor analysis simple rules (IOTA SR)<sup>(1)</sup>

| Rules for predicting malignant tumor (M-rules)                           | Rules for predicting benign tumor (B-rules)                                                     |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| M1 Irregular solid tumor                                                 | B1 Unilocular cyst                                                                              |
| M2 Presence of ascites                                                   | B2 Presence of solid components where the largest solid component has a largest diameter < 7 mm |
| M3 At least four papillary structures                                    | B3 Presence of acoustic shadow                                                                  |
| M4 Irregular multilocular-solid tumor with the largest diameter > 100 mm | B4 Smooth multilocular tumor with the largest diameter < 100 mm                                 |
| M5 Very strong blood flow (color score 4)                                | B5 No blood flow (color score 1)                                                                |

The initial ultrasonography was performed and recorded by expert gynecologists in the Gynecologic Ultrasonography Unit, with experience in gynecologic ultrasound ranging from 5 to 18 years. In cases of inconclusive results, subjective assessment was adjudicated by two experienced ultrasonographers in the Gynecologic Ultrasonography Unit. Discordant results were resolved through consultation with a third ultrasonographer of equivalent expertise.

According to Bast and colleagues, a threshold

of 35 U/mL has widely been adopted as the standard for early detection of ovarian cancer in postmenopausal women<sup>(18)</sup>. Applying the same threshold to premenopausal women leads to a significantly higher incidence of false-positive results. Menopausal status is the primary clinical variable influencing CA125 levels; consequently, a higher diagnostic threshold of 50 U/mL is required for premenopausal women, whereas the conventional 35 U/mL was validated for postmenopausal women<sup>(19)</sup>. For the combined model

of IOTA SR and CA125, lesions categorized as benign by the IOTA SR with a negative CA125 result were classified as benign. Lesions categorized as benign with a positive CA125 result were reclassified as malignant. Lesions categorized as malignant by the IOTA SR, regardless of CA125 status, were classified as malignant.

For IOTA SR inconclusive group with CA125, stratified by menopausal status, lesions that could be directly categorized as benign or malignant required no additional assessment. Lesions classified

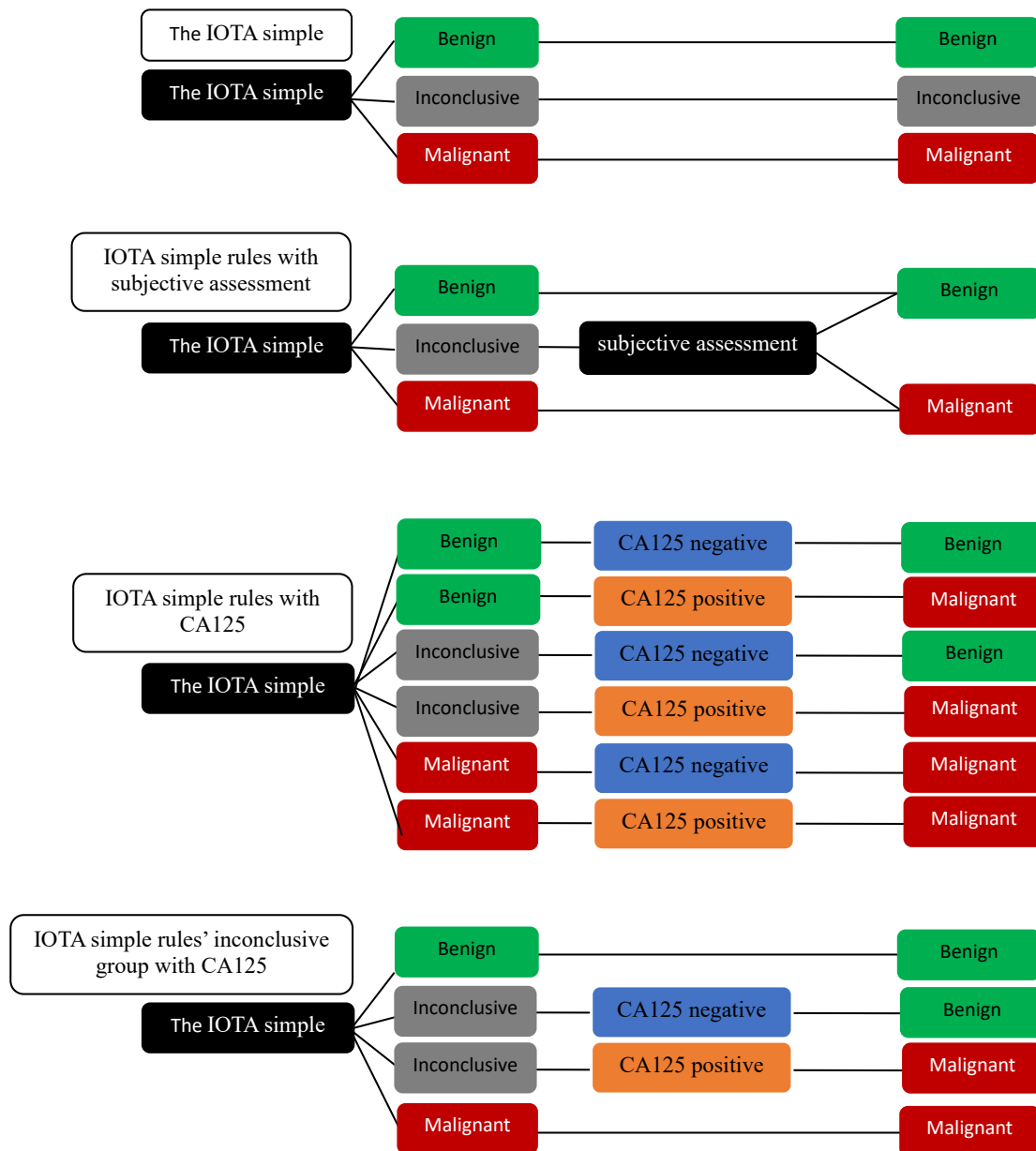
as inconclusive by the IOTA SR with a negative CA125 result were considered benign, whereas those with a positive CA125 result were considered malignant.

Our new optimal CA125 value, derived from the dataset, was applied to the IOTA SR with the new optimal CA125 and to the IOTA SR inconclusive group with the new optimal CA125. The analysis was conducted in the same manner. Table 2 and Fig. 2 provide a summary of the interpretation of each diagnostic approach.

**Table 2.** Interpretation of each diagnostic approach.

| Diagnostic method                                | The IOTA simple rules | CA 125/<br>Optimal CA125 | Subjective<br>assessment | Final<br>group |
|--------------------------------------------------|-----------------------|--------------------------|--------------------------|----------------|
| IOTA simple rules                                |                       |                          |                          |                |
|                                                  | Benign                | -                        | -                        | Benign         |
|                                                  | Malignancy            | -                        | -                        | Malignancy     |
| IOTA simple rules with subjective assessment     |                       |                          |                          |                |
|                                                  | Benign                | -                        | -                        | Benign         |
|                                                  | Inconclusive          | -                        | Benign                   | Benign         |
|                                                  | Inconclusive          | -                        | Malignancy               | Malignancy     |
|                                                  | Malignancy            | -                        | -                        | Malignancy     |
| IOTA simple rules with CA125                     |                       |                          |                          |                |
|                                                  | Benign                | Negative                 | -                        | Benign         |
|                                                  | Benign                | Positive                 | -                        | Malignancy     |
|                                                  | Inconclusive          | Negative                 | -                        | Benign         |
|                                                  | Inconclusive          | Positive                 | -                        | Malignancy     |
|                                                  | Malignancy            | Negative                 | -                        | Malignancy     |
|                                                  | Malignancy            | Positive                 | -                        | Malignancy     |
| IOTA simple rules' inconclusive group with CA125 |                       |                          |                          |                |
|                                                  | Benign                | -                        | -                        | Benign         |
|                                                  | Inconclusive          | Negative                 | -                        | Benign         |
|                                                  | Inconclusive          | Positive                 | -                        | Malignancy     |
|                                                  | Malignancy            | -                        | -                        | Malignancy     |

IOTA: international ovarian tumor analysis, CA125: cancer antigen 125



**Fig. 2.** Interpretation of each diagnostic approach.

Serum CA125 were measured using an electrochemiluminescence immunoassay on the Cobas e601 platform (Roche Diagnostics). The assay demonstrated a lower limit of detection of 0.6 U/mL, with inter-assay and intra-assay coefficients of variation (CV) of 2.5% and 1.6%, respectively.

Histopathological diagnoses served as the gold standard. All excised tissues were examined in the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, following World Health Organization guidelines<sup>(20)</sup>. Malignant tumors were staged according to the International Federation of Gynaecology and Obstetrics

(FIGO)<sup>(21)</sup>. All borderline ovarian tumors were classified as malignant.

Data were analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY) and MedCalc, version 23.2.0 (MedCalc Software, Ostend, Belgium). Descriptive variables were reported as medians, frequencies, or percentages. The diagnostic performance of IOTA SR was evaluated by sensitivity, specificity, positive predictive value, and negative predictive value, along with their 95% confidence intervals (95% CI). Statistical significance was defined as a p value < 0.05. Additionally, the receiver operating characteristic (ROC) curves for each model were plotted, and the area under the ROC curve (AUC)

was calculated to reveal the diagnostic ability and optimal threshold for the CA125 cutoff value. The new optimal CA125 threshold was defined as the cutoff value yielding the highest Youden index. The Hanley and McNeil method was applied for pairwise comparisons between diagnostic methods.

## Results

All 357 patients from the previous study were included without exclusion. The median age of the participants was 43 years. The majority were postmenopausal (71.4%), while premenopausal women accounted for 28.6%. Baseline characteristics and CA125 levels are presented in Table 3.

**Table 3.** Baseline characteristics of the patients according to type of tumor in 357 patients.

|                                  | Total<br>(n = 357) | Benign<br>(n = 296) | Malignant<br>(n = 61) |
|----------------------------------|--------------------|---------------------|-----------------------|
| Age, years                       | 43 (35-53)         | 41 (34-50)          | 52 (43-62)            |
| Menopausal status                |                    |                     |                       |
| Premenopause                     | 102 (28.6)         | 71 (24)             | 26 (42.6)             |
| Postmenopause                    | 255 (71.4)         | 225 (76)            | 35 (57.4)             |
| Parity                           |                    |                     |                       |
| 0                                | 190 (53.2)         | 161 (54.4)          | 29 (47.5)             |
| 1                                | 60 (16.8)          | 50 (16.9)           | 10 (16.4)             |
| 2                                | 78 (21.8)          | 63 (21.3)           | 15 (24.6)             |
| 3 or more                        | 29 (8.2)           | 22 (7.4)            | 7 (11.5)              |
| Family history of ovarian cancer |                    |                     |                       |
| Yes                              | 8 (2.2)            | 7 (2.4)             | 1 (1.6)               |
| No                               | 349 (97.8)         | 289 (97.6)          | 60 (98.4)             |
| Underlying disease               |                    |                     |                       |
| None                             | 263 (73.7)         | 227 (76.7)          | 36 (59)               |
| Other cancer                     | 8 (2.2)            | 6 (2)               | 2 (3.3)               |
| Others                           | 86 (24.1)          | 63 (21.3)           | 23 (37.7)             |
| CA125 level                      | 28.5 (14.5-67.5)   | 24.4 (13.2-50.2)    | 155.8 (43.1-566)      |

Data are presented as median (interquartile range) and n (%) unless otherwise specified.

CA125: cancer antigen 125

Histopathological assessment showed that most adnexal masses in the study were benign (296 cases, 83%) Malignant tumors accounted for 61 cases (17%), including 11 borderline tumors (3%). Among the malignant tumors, 32.8% were stage I, 41.0% were stages II-IV, and five cases (8.2%) were metastatic. Endometrioma was the most prevalent benign adnexal lesion, accounting for 41.6% of cases. In the inconclusive group (41/357), 12.2% (5/41) were malignant: two high-grade serous carcinomas, two clear cell carcinomas, and one borderline mucinous tumor. The most common benign lesion found in the inconclusive group was mature cystic teratoma (13/36). Overall, the IOTA SR could be applied to 316 cases (88.5%). The most common benign feature was unilocular cyst (B1), while the most frequently observed malignant feature in this study was an

irregular multilocular-solid tumor with the largest diameter equal to or greater than 100 mm (M4), observed in 52 cases. The ultrasonographic features of benign and malignant tumors are summarized in Table 4.

The IOTA SR demonstrated the highest diagnostic performance, with an AUC of 0.938 (95% CI, 0.897-0.979), sensitivity of 93.6% (95% CI, 83.3-98.1), and specificity of 94.6% (95% CI, 91.1-97). The IOTA simple rules combined with CA125 showed an AUC of 0.825 (95% CI, 0.776–0.875), which was significantly lower compared with the IOTA simple rules and the IOTA simple rules with subjective assessment. The sensitivity, specificity, negative predictive value, positive predictive value, accuracy, and AUC of each model are presented in Table 5, with corresponding ROC curves in Fig. 3.

**Table 4.** Features of the international ovarian tumor analysis simple rules (IOTA SR)

| Characteristics    | Histopathology (n = 357) |                     |                       |
|--------------------|--------------------------|---------------------|-----------------------|
|                    | Total<br>(n = 357)       | Benign<br>(n = 296) | Malignant<br>(n = 61) |
| Benign features    |                          |                     |                       |
| B1                 | 187                      | 186                 | 1                     |
| B2                 | 1                        | 1                   | 0                     |
| B3                 | 13                       | 11                  | 2                     |
| B4                 | 54                       | 52                  | 2                     |
| B5                 | 93                       | 90                  | 3                     |
| Malignant features |                          |                     |                       |
| M1                 | 6                        | 1                   | 5                     |
| M2                 | 30                       | 5                   | 25                    |
| M3                 | 32                       | 6                   | 26                    |
| M4                 | 52                       | 11                  | 41                    |
| M5                 | 33                       | 5                   | 28                    |

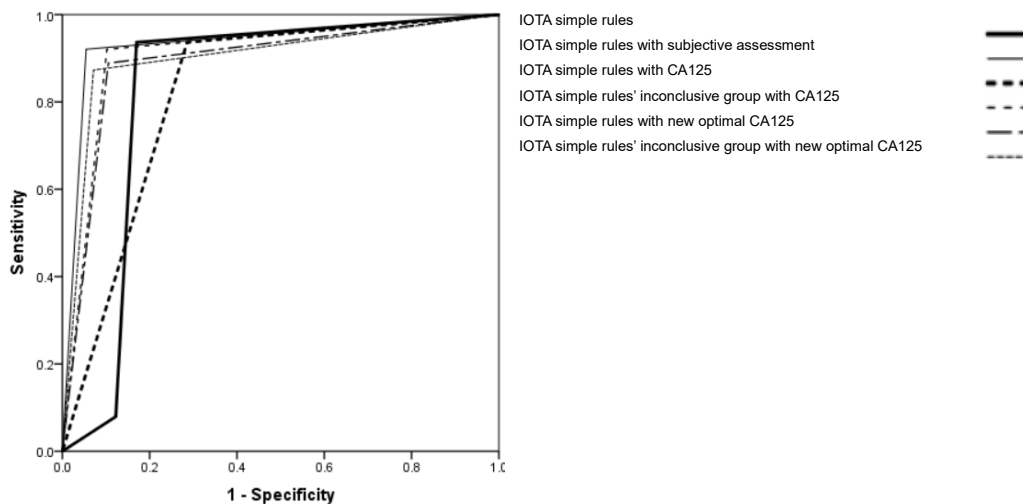
Data are presented as n.

**Table 5.** Diagnostic performance of each diagnostic approach.

|                                                              | <b>Sensitivity, %<br/>(95% CI)</b> | <b>Specificity, %<br/>(95% CI)</b> | <b>PPV, %<br/>(95% CI)</b> | <b>NPV, %<br/>(95% CI)</b> | <b>AUC<br/>(95% CI)</b> |
|--------------------------------------------------------------|------------------------------------|------------------------------------|----------------------------|----------------------------|-------------------------|
| IOTA simple rules                                            | 93.1<br>(83.3-98.1)                | 94.6<br>(91.1-97)                  | 79.4<br>(69.8-86.6)        | 98.4<br>(95.9-99.4)        | 0.938<br>(0.897-0.979)  |
| IOTA simple rules with subjective assessment                 | 92.1<br>(82.4-97.4)                | 94.6<br>(91.3-96.9)                | 78.4<br>(69.1-85.4)        | 98.2<br>(96-99.2)          | 0.933<br>(0.892-0.975)  |
| IOTA simple rules with CA125                                 | 93.6<br>(84.5-98.2)                | 71.4<br>(65.9-76.5)                | 41.3<br>(36.7-46)          | 98.1<br>(95.3-99.2)        | 0.825<br>(0.776-0.875)  |
| IOTA simple rules' inconclusive group with CA125             | 92.1<br>(82.4-97.4)                | 89.8<br>(85.7-93)                  | 65.9<br>(57.7-73.2)        | 98.1<br>(95.8-99.2)        | 0.909<br>(0.866-0.953)  |
| IOTA simple rules with new optimal CA125                     | 64.4<br>(53.4-74.3)                | 97.4<br>(94.7-98.9)                | 88.9<br>(79.1-94.4)        | 89.5<br>(86.5-91.8)        | 0.892<br>(0.842-0.941)  |
| IOTA simple rules' inconclusive group with new optimal CA125 | 72.4<br>(60.9-82)                  | 97.1<br>(94.5-98.8)                | 87.3<br>(77.4-93.2)        | 92.9<br>(90-94.9)          | 0.901<br>(0.850-0.951)  |

Data are presented as presented as percentage.

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, IOTA: international ovarian tumor analysis, CA125: cancer antigen 125

**Fig. 3.** Receiver operating characteristic curves for differentiating between benign and malignant adnexal masses using each diagnostic approach.

Using our dataset, the new optimal CA125 cutoff was determined to be 115 U/mL, which yielded the highest Youden index (0.535). Applying this threshold, the IOTA simple rules' inconclusive group with CA125, the IOTA simple rules with the new optimal CA125, and the IOTA simple rules' inconclusive group achieved AUCs of 0.909 (95% CI, 0.866–0.953),

0.892 (95% CI, 0.842–0.941), and 0.901 (95% CI, 0.850–0.951) respectively. None of these models showed statistically significant differences compared with either the original IOTA simple rules or the IOTA simple rules with subjective assessment. Pairwise comparisons of the diagnostic approaches with p-values are provided in Table 6.

**Table 6.** Pairwise comparison of area under the curves between diagnostic approaches.

|                                                              | IOTA simple rules | IOTA simple rules with subjective assessment | IOTA simple rules with CA125 | IOTA simple rules' inconclusive group with CA125 | IOTA simple rules with new optimal CA125 | IOTA simple rules' inconclusive group with new optimal CA125 |
|--------------------------------------------------------------|-------------------|----------------------------------------------|------------------------------|--------------------------------------------------|------------------------------------------|--------------------------------------------------------------|
| IOTA simple rules                                            |                   | 0.8663                                       | 0.0005*                      | 0.3403                                           | 0.1589                                   | 0.2571                                                       |
| IOTA simple rules with subjective assessment                 | 0.8663            |                                              | 0.0009*                      | 0.4300                                           | 0.2092                                   | 0.2571                                                       |
| IOTA simple rules with CA125                                 | 0.0005*           | 0.0009*                                      |                              | 0.0117*                                          | 0.0581                                   | 0.3270                                                       |
| IOTA simple rules' inconclusive group with CA125             | 0.3403            | 0.4300                                       | 0.0117*                      |                                                  | 0.6097                                   | 0.0351*                                                      |
| IOTA simple rules with new optimal CA125                     | 0.1589            | 0.2092                                       | 0.0581                       | 0.6097                                           |                                          | 0.8143                                                       |
| IOTA simple rules' inconclusive group with new optimal CA125 | 0.2571            | 0.3270                                       | 0.0351*                      | 0.8143                                           | 0.8030                                   |                                                              |

Data was presented in p value.

\* Statistically significant different  $p < 0.05$

AUC: area under the curve, IOTA: international ovarian tumor analysis, CA125: cancer antigen 125

## Discussion

Preoperative diagnosis of adnexal mass is critical for optimal patient management. Ovarian cancer remains a leading cause of cancer-related mortality in women worldwide, largely due to the lack of effective early detection and screening strategies. Multiple diagnostic tools have been developed to differentiate benign from malignant adnexal lesions, including RMI, ADNEX model, O-RADS, and the IOTA SR. According to the 2021 consensus from the European Society of Gynecological Oncology (ESGO), the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), the IOTA, and the European Society for Gynecological Endoscopy (ESGE), subjective assessment by expert ultrasonographers provides the highest diagnostic accuracy in differentiating benign from malignant tumors. However, in settings without expert ultrasonographers, validated ultrasound-based, such as the IOTA SR or the IOTA ADNEX model are valuable alternatives<sup>(10)</sup>. Although the ADNEX model is robust, it requires software support for risk calculation<sup>(17)</sup>, while the IOTA SR are straightforward and do not require additional tools. The IOTA group has consistently been recognized for developing reliable algorithms for ovarian cancer diagnosis, and the simplicity of the simple rules makes them particularly useful for both non-expert and experienced sonographers<sup>(22)</sup>.

In this study, the IOTA SR was applicable in 88.5% of cases, consistent with the findings of a recent systematic review by Awadia et al, who reported an applicability rate of 85.7% across 27 studies involving 7,841 adnexal masses<sup>(23)</sup>. When applicable, the IOTA SR demonstrated high diagnostic performance, with a sensitivity of 93.0% (95% CI 83.0%–98.1%) and specificity of 94.6% (95% CI 91.0%–97.1%), consistent with the pooled estimates reported by Awadia et al (sensitivity and specificity both at 92%)<sup>(23)</sup> and closely match a prospective study

conducted at two tertiary-care hospitals in Spain, which reported sensitivity and specificity of 94.3% and 94.9%, respectively<sup>(24)</sup>.

Secondary analysis enabled application of the IOTA SR model to all patients. The highest accuracy and AUC of 0.933 were achieved when subjective assessment was used as the secondary analysis. To optimize the efficacy of CA125, subgroup analysis was conducted, where CA125 was applied exclusively to the inconclusive results, which were presumed to have a more malignant tendency. The diagnostic accuracy of the IOTA SR is significantly augmented by the addition of serum CA125 for the classification of adnexal masses, according to findings by Phinyo et al<sup>(25)</sup>. The combination of CA125 with the inconclusive group of the IOTA simple rules provided an AUC of 0.909 (95% CI 0.866–0.953).

Ultrasonography is inherently operator-dependent, with outcomes influenced by clinical experience, interpersonal variability, and ultrasonographic machine performance. Although ultrasonography is an operator-dependent tool, the IOTA SR reduces this variability by standardizing assessment and providing a practical tool for preoperative identification of malignant ovarian tumors. Prior studies have reported varying levels of agreement between expert and non-expert ultrasonographers. For example, Alba et al reported only moderate agreement (Cohen's Kappa coefficient 0.50; 95% CI 0.300–0.704) when non-experts applied the IOTA SR<sup>(26)</sup>, while Tinnangwattana et al demonstrated substantial agreement (Cohen's Kappa 0.713–0.884) in a prospective study<sup>(27)</sup>. A recent study in Thailand showed that the IOTA simple rules demonstrated high diagnostic accuracy, even when performed by non-expert examiners<sup>(22)</sup>.

The use of tumor markers may further improve diagnostic performance of the IOTA SR. In our study, combining the IOTA SR with CA125 increased sensitivity but reduced specificity and AUC. We

attempted to optimize the cutoff value of CA125; however, this did not yield any further improvement in test performance. The established cutoff values — greater than 35 U/mL for postmenopausal women and greater than 50 U/mL for premenopausal women. CA125 provides limited benefit except in inconclusive cases. This suggests that the tumor marker could be useful in settings without an expert sonographer, though the small size of our inconclusive group limits the strength of this finding.

The main strength of this study was the use of prospectively collected data, providing comprehensive information. However, limitations included its single-center design, inclusion of only patients who underwent surgery, lack of data on clinical decision-making in non-surgical cases and the variability in ultrasound expertise. Additionally, the small sample size of inconclusive cases may limit the statistical power of this assessment. Future prospective research with a dedicated design is required to further investigate the efficacy of combining CA125 with the IOTA simple rules.

## Conclusion

In summary, an accurate pre-operative diagnosis of ovarian malignancy is crucial to enhance patient outcomes. The IOTA SR was an effective ultrasound-based model for detecting ovarian malignancy. The selective combination of CA125 with the inconclusive group of the IOTA SR demonstrated diagnostic performance comparable to that of subjective assessment. This model is simple, effective, and could be useful in settings where an expert ultrasonographer is unavailable.

## Acknowledgements

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## Authors contribution

K.L.: design, planning, data analysis, and manuscript drafting. P.T.: design, planning, data analysis, and manuscript drafting with critical revisions and supervision. V.P.: design, acquisition of data, data analysis and manuscript drafting with critical revisions.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

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# Effect of Multi-Strain Probiotics on Constipation and Quality of Life in Menopausal Women: A double-blind, Randomized, Placebo-controlled, Single-center trial

Natita Nakapun, M.D.\*,  
Pongrak Boonyanurak, M.D.\*

\* Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand

### ABSTRACT

**Objectives:** To evaluate the short-term efficacy of a multi-strain probiotic supplement (*Bifidobacterium longum*, *B. breve*, *B. lactis*, *B. animalis* TA1, *Lactobacillus paracasei* MSMC 39-1, *L. rhamnosus*, *L. reuteri* TF314, and *L. gasseri*) in improving bowel movement frequency, stool consistency, and menopause-related quality of life in women with functional constipation.

**Materials and Methods:** A double-blind, randomized, placebo-controlled trial was conducted at the gynecology outpatient clinic of a tertiary care hospital in Bangkok, Thailand, between August 2024 and April 2025. For four weeks, 46 women with functional constipation, as defined by Rome IV, were randomized to receive a probiotic or placebo capsule every day. Simple randomization was carried out by a third party, and the allocation was hidden from the participants and researchers. Pretest and posttest questionnaires were used to measure menopause-specific quality of life (MENQOL) and symptoms associated with constipation. Data were analyzed using the intention-to-treat approach.

**Results:** In the probiotics group, the median weekly defecation frequency increased significantly (3.0 to 5.0,  $p = 0.003$ ). Hard stools slightly declined from 32% to 9.1%, although not statistically significant ( $p = 0.200$ ). There were minimal changes in the placebo group. The total MENQOL score, and physical domain improved from  $55.1 \pm 31.2$  to  $40.7 \pm 22.4$  ( $p = 0.012$ ) and from  $34.2 \pm 21.5$  to  $24.4 \pm 14.1$  ( $p = 0.014$ ), respectively, while vasomotor, psychosocial, and sexual domains showed no significant changes. No significant changes occurred in the placebo group. Subgroup analysis of participants over 60 years old showed similar improvements in total score ( $p = 0.041$ ) and physical domain ( $p = 0.029$ ). One participant (4.3%) in the probiotic group discontinued due to bloating.

**Conclusion:** In menopausal women experiencing constipation, a 4-week multi-strain probiotic treatment demonstrated improvements in the frequency of bowel movements, physical domain and total score of menopause-related quality of life. Probiotics may serve as an adjunctive, non-pharmacological approach to support physical well-being in menopausal women.

**Keywords:** functional constipation, menopausal women, probiotic supplementation, menopause-specific quality of life, randomized controlled trial.

## ผลของโพรไบโอติกต่ออาการท้องผูกและคุณภาพชีวิตในสตรีวัยหมดประจำเดือน: การศึกษาแบบสุ่ม มีกลุ่มควบคุมด้วยยาหลอกในลักษณะปกปิดสองทาง ณ ศูนย์เดียว

นทิตา นาคพันธุ์, ปองรัก บุญญานุรักษ์

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อประเมินประสิทธิภาพในระยะสั้นของผลิตภัณฑ์เสริมอาหารที่มีโพรไบโอติกหลายสายพันธุ์ (*Bifidobacterium longum*, *B. breve*, *B. lactis*, *B. animalis* TA1, *Lactobacillus paracasei* MSMC 39-1, *L. rhamnosus*, *L. reuteri* TF314 และ *L. gasseri*) ในการเพิ่มความถี่ของการขับถ่าย, ลักษณะของอุจจาระ และปรับปรุงคุณภาพชีวิตของสตรีวัยหมดประจำเดือนที่มีอาการท้องผูกจากการทำงานผิดปกติของลำไส้

**วัสดุและวิธีการ:** การทดลองแบบสุ่ม มีกลุ่มควบคุมให้ยาหลอก และปกปิดสองฝ่าย ดำเนินการที่คลินิกโรคเรื้อรัง โรงพยาบาลระดับตติยภูมิ กรุงเทพมหานคร ระหว่างเดือนสิงหาคม พ.ศ. 2567 ถึงเมษายน พ.ศ. 2568 ผู้หญิงวัยหมดประจำเดือนจำนวน 46 คน ที่ได้รับการวินิจฉัยว่ามีอาการท้องผูกจากเกณฑ์ Rome IV ถูกสุ่มแบบ 1:1 ให้ได้รับแคปซูลโพรไบโอติกหรือยาหลอก วันละ 1 เม็ด เป็นเวลา 4 สัปดาห์ การสุ่มดำเนินการโดยบุคคลที่สาม และผู้เข้าร่วมกับผู้วิจัยไม่ทราบกลุ่มที่ได้รับการจัดสรร ประเมินอาการเกี่ยวกับระบบขับถ่ายและคุณภาพชีวิตจำเพาะต่อวัยหมดประจำเดือน (MENQOL) โดยทำแบบสอบถามก่อนและหลังการทดลอง วิเคราะห์ข้อมูลตามหลักการวิเคราะห์ตามเจตนาการรักษา (intention-to-treat)

**ผลการศึกษา:** ในกลุ่มโพรไบโอติก ความถี่ในการขับถ่ายต่อสัปดาห์เพิ่มขึ้นอย่างมีนัยสำคัญจาก 3.0 เป็น 5.0 ครั้ง ( $p = 0.003$ ) สัดส่วนของอุจจาระแข็งลดลงจากร้อยละ 32 เหลือ 9.1 ( $p = 0.200$ ) ขณะที่กลุ่มยาหลอกมีการเปลี่ยนแปลงเล็กน้อย คะแนนรวม MENQOL และด้านกายภาพดีขึ้นจาก  $55.1 \pm 31.2$  เป็น  $40.7 \pm 22.4$  ( $p = 0.012$ ) และจาก  $34.2 \pm 21.5$  เป็น  $24.4 \pm 14.1$  ( $p = 0.014$ ) ตามลำดับ ในขณะที่ด้านหลอดเลือดและการควบคุมอุณหภูมิ (vasomotor), ด้านจิตสังคม (psychosocial) และ ด้านเพศสัมพันธ์ (sexual) ไม่พบการเปลี่ยนแปลงอย่างมีนัยสำคัญ และกลุ่มยาหลอกก็ไม่มี การเปลี่ยนแปลงอย่างมีนัยสำคัญเช่นกัน การวิเคราะห์กลุ่มย่อยในผู้ที่มีอายุอย่างน้อย 60 ปี พบแนวโน้มการดีขึ้นเช่นเดียวกัน ผู้เข้าร่วมหนึ่งราย (ร้อยละ 4.3) ในกลุ่มโพรไบโอติกหยุดทดลองเนื่องจากอาการท้องอืด

**สรุป:** ในสตรีวัยหมดประจำเดือนที่มีภาวะท้องผูก การเสริมโพรไบโอติกหลายสายพันธุ์เป็นระยะเวลา 4 สัปดาห์ ช่วยเพิ่มความถี่ในการขับถ่ายอุจจาระและปรับปรุงคุณภาพชีวิตโดยรวมและด้านกายภาพของสตรีวัยหมดประจำเดือนที่มีอาการท้องผูกได้อย่างมีนัยสำคัญ โพรไบโอติกจึงอาจเป็นทางเลือกที่มีประสิทธิภาพโดยไม่ต้องพึ่งพายา เพื่อส่งเสริมสุขภาพทางกายในสตรีวัยหมดประจำเดือน

**คำสำคัญ:** ภาวะท้องผูกจากการทำงาน, สตรีวัยหมดประจำเดือน, การเสริมโพรไบโอติก, คุณภาพชีวิตเฉพาะวัยหมดประจำเดือน, การทดลองแบบสุ่มและมีกลุ่มควบคุม

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## Introduction

Menopause, defined as the absence of menstruation for 12 consecutive months, is a natural process resulting from ovarian failure and declining estrogen levels. Most women experience menopause between the ages of 45 and 55. Hot flashes, sleeplessness, mood swings, vaginal dryness, osteoporosis, and gastrointestinal issues are just a few of the symptoms that can seriously lower quality of life during this transition. Constipation is common and can significantly affect day-to-day functioning. It is probably caused by estrogen's effects on gastrointestinal motility<sup>(1)</sup>. These clinical manifestations affect up to 80% of menopausal women, and it is estimated that by 2030, over 1.2 billion women worldwide will be transitioning into menopause<sup>(2)</sup>.

About 50% of older people suffer from constipation, a common gastrointestinal illness that is acknowledged as a global health concern because of its substantial effects on both physical and psychological well-being<sup>(3)</sup>. Its prevalence rises with age, and it is significantly higher in women, where 33.5% of people over 60 are affected<sup>(4, 5)</sup>. In addition to hormonal changes, several factors, such as chronic illnesses, consuming medications, and physical inactivity, can lead to constipation in older adults<sup>(3)</sup>. Moreover, constipation can lead to issues such as rectal prolapse, fecal impaction, hemorrhoids, and abdominal pain<sup>(4)</sup>.

In the United States, annual over-the-counter laxative expenditures are estimated at \$821 million<sup>(6)</sup>. However, up to 47% of patients express worries about the taste, expense, inconvenience, safety, and adverse effects of these drugs<sup>(7)</sup>. Probiotics have recently drawn interest as an alternate constipation

remedy. According to the World Health Organization (WHO), probiotics are “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”<sup>(8)</sup>. The most studied strains include *Lactobacilli* and *Bifidobacterium*, such as *Lactobacillus acidophilus* LA11-Only, *Lactocaseibacillus rhamnosus* LR22, *Limosilactobacillus reuteri* LE16, *Lactiplantibacillus plantarum* LP-Only, and *Bifidobacterium animalis subsp. lactis* BI516, which significantly increased gastrointestinal transit rate, reduced time to first defecation, and improved stool frequency and weight. According to systematic reviews, certain probiotic strains can decrease gastrointestinal transit time by up to 12 hours, increase the frequency of bowel movements by about 1.5 times per week, and relieve several symptoms associated with constipation when taken at doses ranging from  $10^8$  to  $3 \times 10^{10}$  CFU/day<sup>(9)</sup>.

Menopausal symptoms are associated with gut and vaginal dysbiosis. The estrobolome, a community of microorganisms that control circulating estrogen levels, can be negatively impacted by gut dysbiosis. The beta-glucuronidase enzyme of some probiotics, such as *Bifidobacterium longum*, *Lactobacillus rhamnosus*, *L. reuteri*, and *L. gasseri*, aids in boosting phytoestrogen and estrogen reactivation, which restores estrobolome action. Additionally, these probiotics enhance immunological modulation and lessen systemic inflammation, which may help with hot flashes and other symptoms<sup>(10)</sup>.

Constipation and menopausal symptoms significantly impair both the physical and psychological well-being of menopausal women. This trial aimed to evaluate the short-term impact of an eight-strain probiotic supplement on bowel movement frequency

and stool consistency in menopausal women, because no studies have specifically investigated the use of probiotics for the treatment of constipation in menopausal women. Evaluating the effects of probiotic supplementation on constipation-related symptoms and well-being in these populations was a secondary goal. According to this study, probiotics are a viable non-pharmacological therapeutic option that may help this population become less dependent on pharmaceutical interventions.

## Materials and Methods

This study was a double-blind, randomized, placebo-controlled trial conducted at the gynecology outpatient department of Phramongkutklo Hospital, Bangkok, Thailand, a tertiary care hospital, between August 2024 and April 2025. The Royal Thai Army Medical Department (R091h/67) granted ethical approval. The trial was designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines to ensure the completeness and quality of the randomized controlled trial methodology.

Participants were menopausal women who met Rome IV criteria for functional constipation<sup>(11)</sup>. Menopause was defined as the permanent cessation of menstruation for at least 12 consecutive months<sup>(1)</sup>. Posters were used for recruitment in the gynecology outpatient department, and trained research assistants completed screening. Menopausal women who have gastrointestinal cancers, thyroid conditions being treated, post-radiation intestinal strictures, have used antibiotics, probiotics, prebiotics, or laxatives within the previous two weeks, take more than 1,500 mg of calcium per day, or are unable to communicate in Thai were excluded. All participants provided written informed consent after receiving study information.

Simple randomization, created by a third party using Statistical Applet, was used to assign eligible individuals to receive either a probiotic supplement or a placebo in a 1:1 ratio. Sequentially numbered, opaque, sealed envelopes were used to guarantee

allocation concealment. Healthcare professionals and participants were both blinded to group assignments.

The nutritional supplement product contained eight probiotic strains, prebiotics, and inert excipients totaling 10 billion CFU in each capsule and served as the probiotic in this investigation. The formulation per capsule was as follows: active ingredients consisted of *Bifidobacterium longum* (10 mg), *Bifidobacterium breve* (10 mg), *Bifidobacterium lactis* (10 mg), *Bifidobacterium animalis* TA1 (20 mg), *Lactobacillus paracasei* MSMC 39-1 (20 mg), *Lactobacillus rhamnosus* (10 mg), *Lactobacillus reuteri* TF314 (10 mg), *Lactobacillus gasseri* (10 mg), xylo-oligosaccharides (100 mg), and resistant maltodextrin (100 mg). Among the inactive components were silicon dioxide (20 mg), magnesium stearate (20 mg), and maltodextrin (110 mg). The probiotic capsule and the placebo capsule both contained the same inactive substances. Hard gelatin capsules of size 0 were used to enclose probiotic and placebo capsules. Their looks, packaging, and methods of administration were all the same. For four weeks, participants were told to take one capsule every day before bed. Every participant received behavioral modification counseling, which included eliminating tea intake, maintaining a regular bowel schedule, exercising frequently, eating a high-fiber diet, and drinking two liters of water every day.

Participants who had a widespread rash, tightness in the chest from an allergic reaction, or severe gastrointestinal symptoms such as vomiting or diarrhea that persisted, together with indications of dehydration, had to be excluded from the research.

To assess the frequency of weekly bowel movements, stool consistency, bowel-related symptoms, and menopause-specific quality of life (MENQOL) at baseline and four weeks following supplementation, all participants were asked to fill out questionnaires. The Thai bowel-related symptoms questionnaire, including the Bristol stool form scale<sup>(12)</sup> adapted and permitted by Narathip

Wiwekplern and colleagues<sup>(13)</sup>, was used to evaluate bowel movement frequency, stool consistency, and bowel-related symptoms. Cronbach's alpha coefficient was used to evaluate internal consistency reliability, and the result was 0.87.

The Bristol Stool Form Scale (BSFS) is a validated seven-category scale to classify stool consistency and form, correlating with gut transit time. Type 1 constipation is characterized by distinct, firm lumps that resemble nuts and is a sign of severe constipation. Type 2 constipation is characterized by a lumpy texture and a sausage-like appearance, indicating mild constipation. Type 3 stools have surface cracks and resemble sausages; they are regarded as being within the normal range. Type 4, which is also normal, is soft, smooth, and shaped like a snake or sausage; it is frequently regarded as the perfect form. Type 5 is borderline normal, characterized by soft blobs with distinct borders, and frequently manifests with a propensity for diarrhea. Type 6 is categorized as moderate diarrhea and manifests as fluffy bits with jagged edges. Type 7, which indicates severe diarrhea, is completely liquid and lacks any solid shape. Clinically, types 1 and 2 suggest constipation, types 3 to 5 are regarded as normal, and types 6 and 7 are associated with diarrhea<sup>(12)</sup>.

To measure the quality of life, the Menopause-Specific Quality of Life Questionnaire (MENQOL), a validated self-administered tool designed to evaluate the effect of menopausal symptoms on women's quality of life, was used. It consists of 29 items grouped into four domains: vasomotor (3 items), psychosocial (7 items), physical (16 items), and sexual (3 items). Each item asks whether the symptom was experienced in the past month, and if present, how bothersome it was on a scale from 0 (not bothersome) to 6 (extremely bothersome). The Cronbach's alpha values for the vasomotor, psychosocial, physical, and sexual domains and overall MENQOL score were 0.75, 0.89, 0.93, 0.92, and 0.94, respectively<sup>(14)</sup>. In many domains, the Thai version of the MENQOL showed Cronbach's alpha values between 0.75 and

0.93, indicating acceptable to excellent reliability<sup>(15)</sup>.

The MENQOL questionnaire was selected because it comprehensively evaluates menopause-related quality of life. The physical domain includes items such as fatigue, sleep disturbance, joint stiffness, and bloating — symptoms that may be influenced by changes in bowel function and thus relevant to this study's objectives.

Ghfar et al's study was used to calculate the sample size. 46 individuals (23 in each group) were required to compare two distinct groups using a formula with an 80% likelihood of finding a result and a significance threshold of 0.05, while also accounting for a 30% dropout rate. To compare two independent proportions, researchers used a formula that required a total of 46 participants (23 per group), with a power of 80%, a significance level of 0.05, and accounting for a 30% dropout rate.

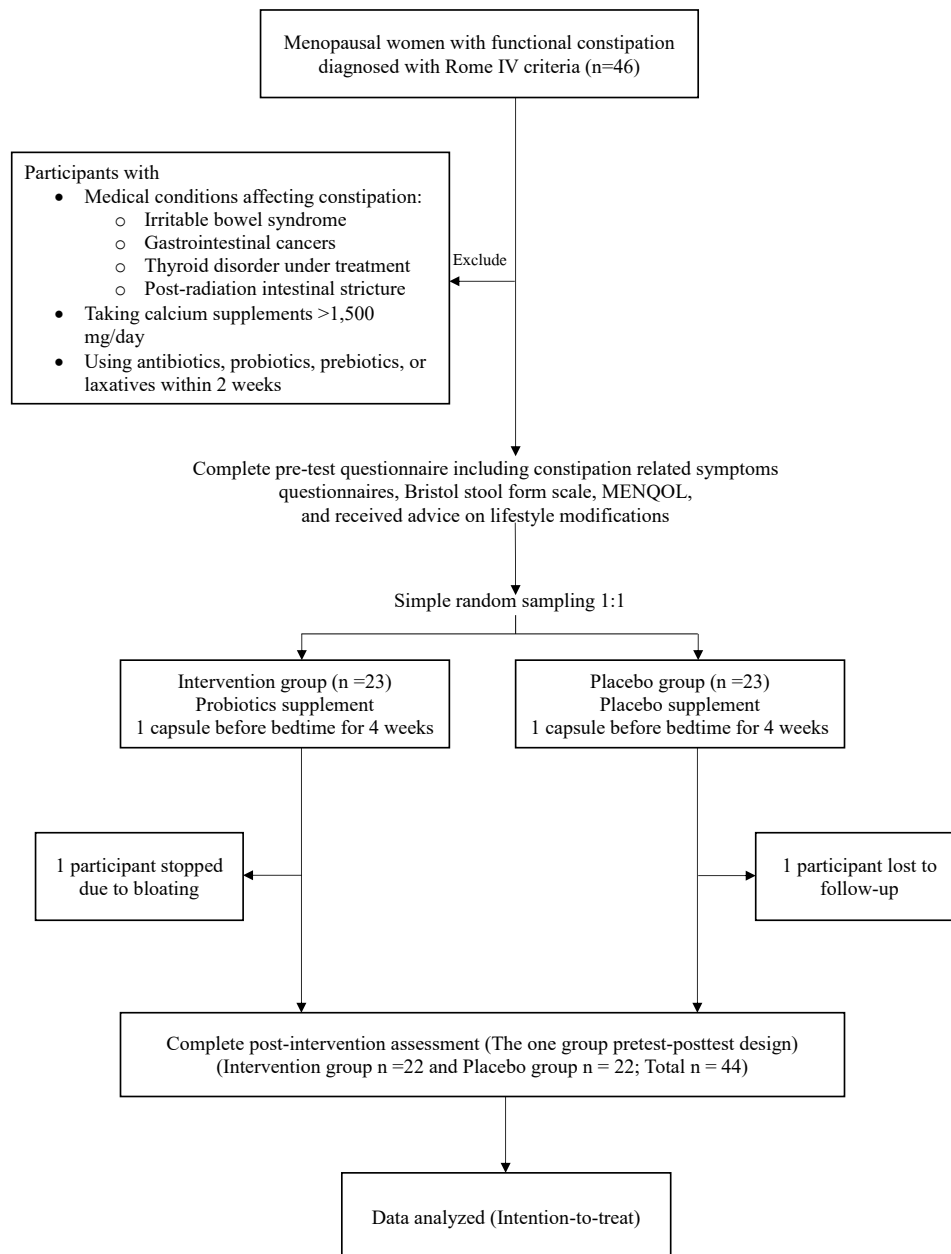
For all statistical analyses, R 4.4.1 was used. For categorical data, participant characteristics were expressed as frequency and percentage. For continuous data, they were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), as applicable. The Shapiro-Wilk test was used to evaluate the distribution of quantitative variables. The Wilcoxon signed-rank test for non-parametric distributions and the dependent t-test for parametric distributions were used to compare continuous data across the two groups. The Fisher's exact test or the chi-square test, if applicable, was used to evaluate categorical variables. The same statistical tests were used to perform subgroup analysis for participants who were 60 years of age and older. Two-tailed statistical analyses were performed, and p values less than 0.05 were deemed statistically significant. No missing data were reported during the study. All analyses followed the intention-to-treat principle.

## Results

In this study, 46 volunteers were recruited, including 23 participants in each group, and they were

randomly randomized to receive either a probiotic or a placebo. Due to bloating, one probiotic group participant had to be excluded. The study details are shown in Fig. 1. Baseline characteristics of eligible participants are presented in Table 1. In general, the majority of clinical, dietary, exercise, and demographic factors were similar between the intervention and

placebo groups. Nevertheless, the median age was significantly lower in the intervention group (61 years, IQR 55, 68) compared to the placebo group (67 years, IQR 60, 78) ( $p = 0.036$ ). Other demographic data showed no significant differences between groups. Thus, the two groups' initial characteristics were identical overall, with the exception of age.



**Fig. 1.** Flow of participant enrollment.

**Table 1.** Baseline characteristics of participants.

| Characteristic                                    | Placebo (n = 22)   | Intervention (n = 22) | p value            |
|---------------------------------------------------|--------------------|-----------------------|--------------------|
|                                                   | n (%)              | n (%)                 |                    |
| Age (years)                                       |                    |                       | 0.116 <sup>d</sup> |
| < 60                                              | 5 (22.7)           | 11 (50.0)             |                    |
| ≥ 60                                              | 17 (77.3)          | 11 (50.0)             |                    |
| Median (IQR)                                      | 67 (60, 78)        | 61 (55, 68)           | 0.036 <sup>b</sup> |
| Body mass index <sup>a</sup> (kg/m <sup>2</sup> ) | 25.5 (22.4, 27.3)  | 24.4 (22.9, 26.4)     | 0.898 <sup>b</sup> |
| Marital status                                    |                    |                       | 0.630 <sup>c</sup> |
| Single                                            | 5 (22.7%)          | 3 (13.6%)             |                    |
| Married                                           | 14 (63.6%)         | 14 (63.6%)            |                    |
| Widowed                                           | 3 (13.6%)          | 3 (13.6%)             |                    |
| Divorce                                           | 0 (0.0%)           | 2 (9.1%)              |                    |
| Underlying diseases                               |                    |                       |                    |
| Hypertension                                      | 7 (31.8%)          | 5 (22.7%)             | 0.498 <sup>d</sup> |
| Diabetes mellitus                                 | 2 (9.1%)           | 3 (13.6%)             | 1.000 <sup>c</sup> |
| Dyslipidemia                                      | 6 (27.3%)          | 8 (36.4%)             | 0.517 <sup>d</sup> |
| Other                                             | 7 (31.8%)          | 2 (9.1%)              | 0.132 <sup>c</sup> |
| Occupation                                        |                    |                       | 0.347 <sup>c</sup> |
| Government                                        | 6 (27.3%)          | 3 (13.6%)             |                    |
| Self employed                                     | 0 (0.0%)           | 1 (4.5%)              |                    |
| Trading                                           | 2 (9.1%)           | 5 (22.7%)             |                    |
| Unemployed                                        | 14 (63.6%)         | 13 (59.1%)            |                    |
| Educational level                                 |                    |                       | 0.724 <sup>d</sup> |
| Primary school                                    | 4 (18.2%)          | 8 (36.4%)             |                    |
| Secondary/vocational school                       | 8 (36.4%)          | 6 (27.3%)             |                    |
| Bachelor's degree or higher                       | 10 (45.5%)         | 8 (36.4%)             |                    |
| Beverage intake <sup>a</sup>                      |                    |                       |                    |
| Tea (cup per week)                                | 0.00 (0.00, 2.00)  | 0.00 (0.00, 0.00)     | 0.522 <sup>b</sup> |
| Coffee (cup per week)                             | 5.0 (0.0, 7.0)     | 7.0 (0.0, 7.0)        | 0.245 <sup>b</sup> |
| Water (glass a day)                               | 8.00 (6.00, 10.00) | 6.00 (5.00, 8.00)     | 0.225 <sup>b</sup> |
| Consumed dietary fiber intake frequency per day   |                    |                       | 0.701 <sup>c</sup> |
| Everyday                                          | 7 (31.8%)          | 10 (45.5%)            |                    |
| Frequently (5-6 times a week)                     | 5 (22.7%)          | 5 (22.7%)             |                    |
| Occasionally (3-4 times a week)                   | 4 (18.2%)          | 4 (18.2%)             |                    |
| Rarely (1-2 times a week)                         | 6 (27.3%)          | 3 (13.6%)             |                    |
| Consumed dietary fiber per meal                   |                    |                       | 0.680 <sup>c</sup> |
| Half                                              | 8 (36.4%)          | 9 (40.9%)             |                    |
| Less than half                                    | 8 (36.4%)          | 7 (31.8%)             |                    |
| More than half                                    | 4 (18.2%)          | 6 (27.3%)             |                    |
| None                                              | 2 (9.1%)           | 0 (0.0%)              |                    |
| Exercise <sup>a</sup> (minutes/week)              | 55 (0, 140)        | 33 (0, 210)           | 0.942 <sup>b</sup> |

IQR: interquartile range

<sup>a</sup> Median (Q1, Q3)<sup>b</sup> Wilcoxon rank sum test; <sup>c</sup> Fisher's exact test; <sup>d</sup> Pearson's Chi-squared test

Table 2 displays the bowel-related symptoms before and after the 4-week intervention for the

intervention and placebo groups. The median (IQR) defecation frequency per week significantly increased

in the intervention group from 3.0 (2.0, 3.0) to 5.0 (4.0, 7.0) ( $p = 0.003$ ). The placebo group also showed an improvement from 2.0 (2.0, 3.0) to 3.5 (2.0, 4.0) ( $p = 0.049$ ). The proportion of participants requiring enemas decreased from 14% to 4.5% in the placebo group and from 4.5% to 0% in the intervention group. Additionally, in the intervention group, the number of participants who no longer delayed bowel movements increased from 14 (64%) to 20 (91%) ( $p = 0.080$ ), without significant difference.

In terms of stool consistency, the number of participants with hard stools (BSFS types 1–2) went

down from 32% to 9.1% in the intervention group, while it stayed the same in the placebo group. Normal stools (BSFS types 3–5) increased from 55% to 64% in the intervention group and from 41% to 50% in the placebo group. Despite the fact that these modifications benefited the intervention group, there was no statistically significant difference between the pre- and post-treatment groups ( $p = 0.200$ ). Although they did not approach statistical significance, other symptoms such as straining, incomplete evacuation, bloating, feeling of obstruction, and gas showed numerical improvements in the intervention group.

**Table 2.** Bowel-related symptoms before and after treatment between the placebo and intervention groups.

| Characteristic                                        | Placebo (n = 22) |                | p value            | Intervention (n = 22) |                | p value            |
|-------------------------------------------------------|------------------|----------------|--------------------|-----------------------|----------------|--------------------|
|                                                       | Pre-treatment    | Post-treatment |                    | Pre-treatment         | Post-treatment |                    |
|                                                       | n (%)            | n (%)          |                    | n (%)                 | n (%)          |                    |
| Number of defecations over the past week <sup>a</sup> | 2.0 (2.0, 3.0)   | 3.5 (2.0, 4.0) | 0.049 <sup>b</sup> | 3.0 (2.0, 3.0)        | 5.0 (4.0, 7.0) | 0.003 <sup>b</sup> |
| Use of enema in the past month                        | 3 (14%)          | 1 (4.5%)       | 0.600 <sup>c</sup> | 1 (4.5%)              | 0 (0%)         | 1.000 <sup>c</sup> |
| Frequency of holding defecation per week              |                  |                | 1.000 <sup>c</sup> |                       |                | 0.080 <sup>c</sup> |
| Never                                                 | 15 (68%)         | 16 (73%)       |                    | 14 (64%)              | 20 (91%)       |                    |
| Sometimes (1 to 2 times)                              | 1 (4.5%)         | 0 (0%)         |                    | 3 (14%)               | 0 (0%)         |                    |
| Occasionally (3 to 4 times)                           | 4 (18%)          | 3 (14%)        |                    | 4 (18%)               | 2 (9.1%)       |                    |
| Frequently (5 to 6 times)                             | 2 (9.1%)         | 3 (14%)        |                    | 1 (4.5%)              | 0 (0%)         |                    |
| Blood in the stool                                    | 1 (4.5%)         | 1 (4.5%)       | 1.000 <sup>c</sup> | 1 (4.5%)              | 1 (4.5%)       | 1.000 <sup>c</sup> |
| Bristol stool form scale                              |                  |                | 0.700 <sup>c</sup> |                       |                | 0.200 <sup>c</sup> |
| Hard (type 1 or 2)                                    | 10 (45%)         | 10 (45%)       |                    | 7 (32%)               | 2 (9.1%)       |                    |
| Normal (type 3,4 or 5)                                | 9 (41%)          | 11 (50%)       |                    | 12 (55%)              | 14 (64%)       |                    |
| Watery (type 6 or 7)                                  | 3 (14%)          | 1 (4.5%)       |                    | 3 (14%)               | 6 (27%)        |                    |
| Constipation assessment form (out of 10) <sup>a</sup> |                  |                |                    |                       |                |                    |
| Straining                                             | 5.0 (3.0, 7.0)   | 5.0 (3.0, 7.0) | 1.000 <sup>b</sup> | 4.0 (0.0, 5.0)        | 2.0 (0.0, 4.0) | 0.600 <sup>b</sup> |
| Incomplete evacuation                                 | 5.0 (3.0, 7.0)   | 4.0 (3.0, 6.0) | 0.700 <sup>b</sup> | 3.0 (0.0, 5.0)        | 0.5 (0.0, 3.0) | 0.200 <sup>b</sup> |
| Obstruction sensation                                 | 3.0 (0.0, 7.0)   | 3.0 (0.0, 6.0) | 0.800 <sup>b</sup> | 2.0 (0.0, 6.0)        | 0.0 (0.0, 3.0) | 0.065 <sup>b</sup> |
| Defecation satisfaction                               | 5.0 (4.0, 7.0)   | 7.0 (6.0, 8.0) | 0.006 <sup>b</sup> | 7.0 (5.0, 8.0)        | 8.0 (6.0, 8.0) | 0.200 <sup>b</sup> |
| Bloating                                              | 4.0 (0.0, 7.0)   | 1.0 (0.0, 5.0) | 0.300 <sup>b</sup> | 1.5 (0.0, 4.0)        | 0.0 (0.0, 2.0) | 0.200 <sup>b</sup> |
| Belching frequency                                    | 1.5 (0.0, 5.0)   | 2.0 (0.0, 5.0) | 1.000 <sup>b</sup> | 2.0 (0.0, 5.0)        | 1.0 (0.0, 2.0) | 0.400 <sup>b</sup> |
| Appetite loss                                         | 3.5 (2.0, 5.0)   | 2.0 (0.0, 5.0) | 0.120 <sup>b</sup> | 1.0 (0.0, 3.0)        | 0.0 (0.0, 2.0) | 0.200 <sup>b</sup> |
| Flatulence                                            | 4.0 (2.0, 6.0)   | 4.5 (3.0, 7.0) | 0.800 <sup>b</sup> | 4.0 (2.0, 5.0)        | 3.0 (2.0, 6.0) | 1.000 <sup>b</sup> |

<sup>a</sup> median (Q1, Q3)

<sup>b</sup> Wilcoxon rank sum test; <sup>c</sup> Fisher's exact test

Table 3 presents the Menopause-Specific Quality of Life (MENQOL) scores for both the placebo and intervention groups before and after the 4-week intervention. The total MENQOL score in the intervention group significantly decreased from

55.1 ± 31.2 to 40.7 ± 22.4 ( $p = 0.012$ ), reflecting an improvement in menopause-specific quality of life. In contrast, no significant change was observed in the placebo group (64.9 ± 40.3 to 65.5 ± 42.7,  $p = 0.873$ ) (Fig. 2). The physical domain in the intervention group

also showed a significant improvement ( $34.2 \pm 21.5$  to  $24.4 \pm 14.1$ ,  $p = 0.014$ ), indicating reductions in symptoms such as decreased energy, fatigue, muscle or joint stiffness, and difficulty sleeping. The vasomotor

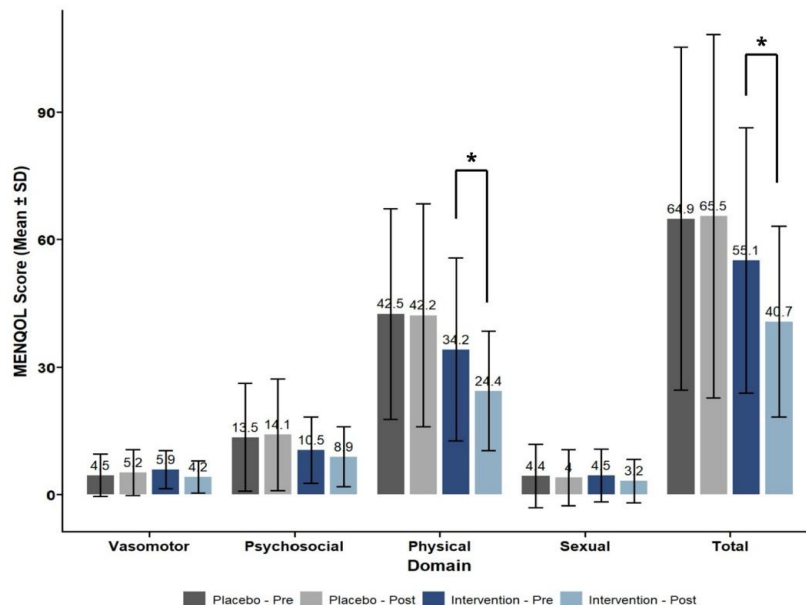
domain showed a pattern toward improvement ( $5.9 \pm 4.5$  to  $4.2 \pm 3.8$ ,  $p = 0.066$ ). Conversely, the placebo group did not show any significant changes in their MENQOL score.

**Table 3.** MENQOL scores before and after treatment between the placebo and intervention groups.

| Characteristic | Placebo (n = 22) |                 | p value <sup>a</sup> | Intervention (n = 22) |                 | p value <sup>a</sup> |
|----------------|------------------|-----------------|----------------------|-----------------------|-----------------|----------------------|
|                | Pre-treatment    | Post-treatment  |                      | Pre-treatment         | Post-treatment  |                      |
|                | mean $\pm$ SD    | mean $\pm$ SD   |                      | mean $\pm$ SD         | mean $\pm$ SD   |                      |
| Vasomotor      | 4.5 $\pm$ 5.0    | 5.2 $\pm$ 5.4   | 0.189                | 5.9 $\pm$ 4.5         | 4.2 $\pm$ 3.8   | 0.066                |
| Psychosocial   | 13.5 $\pm$ 12.7  | 14.1 $\pm$ 13.2 | 0.587                | 10.5 $\pm$ 7.8        | 8.9 $\pm$ 7.1   | 0.226                |
| Physical       | 42.5 $\pm$ 24.8  | 42.2 $\pm$ 26.2 | 0.898                | 34.2 $\pm$ 21.5       | 24.4 $\pm$ 14.1 | 0.014                |
| Sexual         | 4.4 $\pm$ 7.5    | 4.0 $\pm$ 6.6   | 0.762                | 4.5 $\pm$ 6.2         | 3.2 $\pm$ 5.1   | 0.243                |
| Total          | 64.9 $\pm$ 40.3  | 65.5 $\pm$ 42.7 | 0.873                | 55.1 $\pm$ 31.2       | 40.7 $\pm$ 22.4 | 0.012                |

MENQOL: menopause-specific quality of life, SD: standard deviation.

<sup>a</sup> Dependent sample t-test



**Fig. 2.** Average MENQOL scores before and after 4 weeks of intervention.

The subgroup analysis of participants who were 60 years of age or older revealed similar trends to the analysis as a whole. The probiotic group showed a notable increase in how often they had bowel movements, going from an average of 3.0 (IQR 2.0, 3.0) to 5.0 (IQR 3.0, 7.0) times a week ( $p = 0.018$ ); their physical MENQOL scores improved from  $39.7 \pm 22.7$  to  $27.4 \pm 15.7$  ( $p = 0.029$ ), and their

total MENQOL score went down from  $62.9 \pm 35.6$  to  $45.5 \pm 24.5$  ( $p = 0.041$ ); meanwhile, the placebo group had very little change. In addition, stool consistency also improved in the probiotic group, with a reduction in hard stools (from 36% to 9.1%) and an increase in normal stools (from 55% to 82%). However, these changes did not reach statistical significance.

## Discussion

The effects of probiotic supplements on constipation and menopausal women's quality of life were examined in this randomized, double-blind, placebo-controlled study. Following a 4-week intervention, the probiotic group's stool frequency increased, and their MENQOL score's physical domain and overall score also improved. Bloating caused one person (4.3%) in the probiotics group to stop taking them.

This study found that in menopausal women with functional constipation, taking probiotic supplements increases the frequency of bowel movements and decreases hard stools. These results were consistent with earlier studies conducted on older adults. In older adults, Ghafar et al reported that supplementation with *Lactobacillus* and *Bifidobacterium* species improved stool form and evacuation within seven days, and Katarina Fehir Šola et al found increased bowel frequency after 12 weeks without adverse effects<sup>(16, 17)</sup>. In younger adults, Ojetti et al showed that *Lactobacillus reuteri* increased the frequency of bowel movements to 5.28 per week compared to 3.89 per week ( $p < 0.05$ ), although changes in stool form were not significant<sup>(18)</sup>. The efficacy of probiotics did not differ notably between genders or age groups, consistent with previous studies, suggesting that the benefits of probiotics are generally consistent across populations. Furthermore, the current study found that blockage sensation has improved, which has not often been the case in earlier research.

Even after age stratification, this study showed increases in quality of life, especially in the physical domain of the MENQOL score. These results imply that, in addition to enhancing gastrointestinal function, probiotics may also reduce physical menopausal symptoms like fatigue, joint pain, and muscle stiffness. In a related study, Sawada et al evaluated *Lactobacillus gasseri* CP2305 in 106 Japanese women aged 40–60 over six menstrual cycles and found a 75% reduction in Simplified Menopausal Index (SMI) scores in the probiotic group, compared

to 55% in the placebo group<sup>(19)</sup>. Vasomotor, psychological, and physical symptoms are all included in the SMI, but it does not measure menopause-related quality of life in the same multifaceted way as MENQOL. Therefore, more research is necessary to directly compare how probiotics affect MENQOL and SMI results in order to better understand how they affect menopausal well-being in general.

Increased formation of free radicals and oxidative imbalance are linked to menopausal symptoms, which are mainly caused by a significant drop in estrogen levels<sup>(15)</sup>. Probiotics may help reduce age-related oxidative stress because of their immunomodulatory and antioxidant qualities. Likewise, probiotics can increase the colonization of *Lactobacillus* in the vaginal microbiome, which may lower the risk of genitourinary syndrome of menopause and urinary tract infections, both of which are associated with estrogen deprivation<sup>(20, 21)</sup>. The physical gains seen in this study could be partially explained by these mechanisms.

Although there is still little data specifically related to menopausal women, the results of this study were in line with earlier studies that have shown the benefits of probiotics in promoting bowel regularity and general well-being. This trial's double-blind, placebo-controlled design, validated outcome measures, and use of the Rome IV criteria for identifying functional constipation are among its strong points. The Rome IV criteria offer a highly detailed, standardized, symptom-based diagnostic framework that guarantees proper participant selection and improves the dependability and comparability of study results. Significant increases in the physical domain and overall quality of life were seen when the MENQOL questionnaire was used, which is noteworthy because these outcomes have rarely been covered in previous probiotic studies with menopausal women.

Although the extent of the improvement was modest, it may hold clinical relevance. The median frequency of bowel movements increased from three

to five times per week, suggesting a practical improvement toward normal bowel regularity. The physical domain of the MENQOL score decreased by 9.8 points (29%) and the total MENQOL score by 14.4 points (26%), both indicating enhanced physical comfort. Previous studies have suggested that a reduction of approximately 10 points in MENQOL may represent a clinically meaningful improvement in the perceived quality of life among menopausal women. Therefore, the present intervention may contribute to better physical well-being<sup>(22)</sup>.

Importantly, the use of quality-of-life assessment tools is well supported in Thai populations. Previous Thai research has demonstrated the value of evaluating health-related quality of life among menopausal women with urogenital symptoms by using the incontinence-specific quality of life (I-QOL) questionnaire<sup>(23)</sup>. This Thai study has primarily focused on urinary incontinence and its impact on the quality of life of menopausal women. The present study extends this concept to menopausal women with functional constipation, supporting the application of validated tools such as MENQOL in Thai menopausal research and reflecting its relevance in local clinical settings.

However, several limitations should be noted. First, the analysis's statistical power might have been reduced by the small sample size. Second, it is possible that the 4-week trial period was not long enough to identify improvements in vasomotor symptoms, constipation-related symptoms, and sexual function; these might need longer treatment durations to show noticeable improvements; therefore, further studies with longer treatment durations are warranted to better evaluate these outcomes. Furthermore, subjective results might have been impacted by an age gap between the two groups; to reduce this potential confounder, future research should use statistical adjustments or age-matched randomization. In addition, enema use, which could potentially affect bowel-related outcomes, was assessed both before and after the intervention to control its confounding effect. The mean frequency

of enema use was comparable between the two groups at baseline and showed no significant change after the intervention, indicating that it was unlikely to have influenced the primary outcomes of bowel movement frequency or stool consistency.

Despite these limitations, subgroup analysis revealed reliable outcomes for persons over 60. To validate these findings and evaluate their wider implications in menopausal care, new studies with larger sample sizes for greater statistical power, longer follow-up periods, and balanced age distribution are necessary. Additionally, prior randomized controlled trials supported the continuous use of probiotics without treatment pauses for menopausal symptoms and constipation<sup>(9)</sup>.

## Conclusion

According to this randomized, double-blind, placebo-controlled study, a 4-week course of an 8-strain probiotic supplement significantly increased the frequency of bowel movements, the overall MENQOL score, and the physical domain of the MENQOL score among menopausal women with functional constipation. These results confirm that probiotics are a non-pharmacological way to treat somatic menopausal symptoms and constipation.

## Acknowledgements

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## OBSTETRICS

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# Effect of Oral Ginger with Early Feeding versus Early Feeding Alone on Breast Milk Volume in Scheduled Cesarean Section: A randomized controlled trial

Prapabhorn Puenprom, M.D.\*,  
Rungruedee Jeerasap, M.D.\*

\* *Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

### ABSTRACT

**Objectives:** To evaluate the effect of oral ginger supplementation, in combination with early maternal oral feeding, on breast milk volume in women undergoing scheduled Cesarean section.

**Materials and Methods:** This randomized, double-blind, placebo-controlled trial included women scheduled for Cesarean section. Participants were allocated into two groups. At 6 hours postpartum, the intervention group received 200 mL of a sweetened clear solution along with oral ginger capsules (1.5 g daily in three divided doses), while the control group received the same solution with identical placebo capsules (1.5 g fine brown sugar). The primary outcome was breast milk volume, measured at 72 hours postpartum after a two-hour breast emptying period.

**Results:** Between August 2024 and May 2025, a total of 84 participants were randomized (n = 42 per group). The ginger group showed a significantly higher median breast milk volume at 72 hours postpartum (20 mL [interquartile range, IQR 14, 35]) compared to the placebo group (10.5 mL [IQR 9, 15],  $p < 0.001$ ). The self-reported time to onset of lactation was significantly shorter in the ginger group (59 hours vs 69 hours,  $p < 0.001$ ). No serious adverse events were noted.

**Conclusion:** Oral ginger supplementation combined with early maternal oral feeding significantly increased breast milk volume and shortened the time to the onset of lactation in women following scheduled Cesarean section without serious adverse events.

**Keywords:** ginger, early feeding, cesarean section, breastfeeding, lactation.

**Correspondence to:** *Prapabhorn Puenprom, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. E-mail: Join.prapabhorn@gmail.com*

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**ประสิทธิภาพของการรับประทานซิงเสริมร่วมกับการรับประทานอาหารเร็วเปรียบเทียบกับรับประทานอาหารเช้าอย่างเดียวย่อปริมาณน้ำนมหลังการผ่าตัดคลอดตามกำหนดการ: : การทดลองแบบสุ่มที่มีกลุ่มควบคุม**

ประภาพร พันพรม, รุ่งฤดี จีระทรัพย์

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาประสิทธิภาพของการรับประทานซิงเสริมร่วมกับการเริ่มรับประทานอาหารหลังผ่าตัดคลอดเร็วต่อปริมาณน้ำนมในมารดาที่ผ่าตัดคลอดตามกำหนดการ

**วัสดุและวิธีการ:** การทดลองแบบสุ่มที่มีกลุ่มควบคุมในมารดาหลังผ่าตัดคลอดตามกำหนดการ แบ่งเป็น 2 กลุ่ม 6 ชั่วโมงหลังผ่าตัดคลอด กลุ่มทดลองได้รับสารละลายไฮโดรออกไซด์ของแคลเซียม (ซึ่งขนาด 1.5 กรัมต่อวัน แบ่งรับประทานวันละ 3 ครั้ง) และกลุ่มควบคุมได้รับสารละลายเดียวกันร่วมกับยาหลอกที่ลักษณะเหมือนกัน (น้ำตาลทรายแดงผงละเอียดขนาด 1.5 กรัมต่อวัน) วัดผลเป็นปริมาณน้ำนมที่ 72 ชั่วโมงหลังคลอด ภายหลังการปั้มนมจนเกลี้ยงเต้าสองชั่วโมง

**ผลการศึกษา:** มารดาจำนวน 84 รายที่ได้รับการสุ่ม (กลุ่มละ 42 ราย) ระหว่างเดือนสิงหาคม 2567 ถึงพฤษภาคม 2568 กลุ่มที่รับประทานซิงมีค่ามัธยฐานของปริมาณน้ำนมที่ 72 ชั่วโมงหลังคลอดสูงกว่าอย่างมีนัยสำคัญทางสถิติ (20 มล. [interquartile range, IQR 14, 35]) เมื่อเปรียบเทียบกับกลุ่มยาหลอก (10.5 มล. [IQR 9, 15],  $p < 0.001$ ) เวลาการเริ่มหลังของน้ำนมเต็มเต้าน้อยลงอย่างมีนัยสำคัญในกลุ่มที่ได้รับการรับประทานซิง (59 ชั่วโมง เปรียบเทียบกับ 69 ชั่วโมง,  $p < 0.001$ ) โดยไม่พบภาวะแทรกซ้อนที่รุนแรง

**สรุป:** การรับประทานซิงเสริมร่วมกับการเริ่มรับประทานอาหารเร็วช่วยเพิ่มปริมาณน้ำนม และลดระยะเวลาเวลาในการเริ่มมีหลังของน้ำนมเต็มเต้านในมารดาหลังการผ่าตัดคลอดแบบมีกำหนดการได้อย่างมีนัยสำคัญ โดยไม่พบเหตุการณ์ไม่พึงประสงค์ที่รุนแรง

**คำสำคัญ:** ซิง, การรับประทานอาหารเช้า, กำหนดการ, การผ่าตัดคลอด, การเลี้ยงลูกด้วยนมแม่

## Introduction

Cesarean section (C-section) is a significant barrier to successful lactation, and its increasing prevalence, including in Thailand, is a growing concern<sup>(1, 2)</sup>. The procedure can indirectly impact the initiation and continuation of breastfeeding due to several factors, namely, delayed skin-to-skin contact, postoperative pain and recovery, mother-infant separation, and heightened maternal stress or anxiety, all of which can disrupt the crucial early establishment of breastfeeding<sup>(3, 4)</sup>.

Two interventions that have shown promise in stimulating lactation are early oral feeding and ginger. Early oral feeding, as recommended by the enhanced recovery after surgery (ERAS) protocol, helps stimulate bowel function and promotes a faster recovery and ambulation<sup>(5)</sup>. Concurrently, ginger (*Zingiber officinale*) contains bioactive compounds such as gingerols, shogaol, zingerone, and paradol<sup>(6)</sup>. These compounds have multiple therapeutic properties, including vasodilatory effects that increase blood flow to the breasts, potentially enhancing milk production<sup>(7, 8)</sup>. Furthermore, several studies have demonstrated ginger's efficacy in improving gastrointestinal motility, with significant evidence showing a reduction in postoperative ileus following C-sections<sup>(9-11)</sup>. Consequently, ginger is highly compatible with early oral feeding protocols. The United States Food and Drug Administration (FDA) has approved ginger as safe for use during pregnancy and lactation<sup>(12)</sup>.

Existing research studies have demonstrated that initiating oral intake within 30 minutes to 8 hours after C-section is safe and can stimulate lactation<sup>(13-15)</sup>. Although a systematic review in 2021 found that it may be beneficial for those who have had a vaginal delivery, there was no strong evidence that ginger alone increases human breast milk volume in mothers who have had a C-section<sup>(16)</sup>. Interestingly, a 2022 study found that combining ginger with early feeding significantly stimulated lactation in mothers who underwent an emergency C-section<sup>(17)</sup>. However, the

outcome measurement of this combination has been shown to shorten the onset of lactation (OL) based on maternal perception, which is subjective and relies on self-reported symptoms. Furthermore, no studies have investigated this combined intervention specifically in women undergoing scheduled C-sections, which is often characterized by a delayed onset of lactation, delayed initiation, and lower rates of breastfeeding compared to those who have emergency C-sections<sup>(18, 19)</sup>. Therefore, this study aimed to evaluate the effect of combining ginger with early feeding on lactation by objectively measuring breast milk volume in women undergoing a scheduled C-section.

## Materials and Methods

A randomized, double-blind, placebo-controlled trial was conducted at Khon Kaen Hospital, Thailand, between August 2024 and May 2025. The study received ethical approval from the Khon Kaen Hospital Institutional Review Board (IRB) for Human Research (Reference No. KEF67014). Before data collection, the trial was registered with the Thai Clinical Trials Registry (Registration No. TCTR20240817006).

Eligible participants included term singleton pregnant women aged 18–45 years who underwent a scheduled C-section under spinal anesthesia with intrathecal morphine between 08:00 a.m. and 04:00 p.m. They were required to have delivered a healthy newborn ( $\geq 2,500$  g and an Apgar score  $\geq 7$  at 1 and 5 minutes, with no major congenital anomalies<sup>(20, 21)</sup>), intended to breastfeed, and be able to speak and understand the Thai language.

Participants were excluded if they had any contraindications to breastfeeding (e.g., maternal human immunodeficiency virus, active tuberculosis, illegal drug use, or current use of antiretroviral medications). Additional exclusion criteria included a history of breast cancer or prior breast surgery, uncontrolled medical or obstetric complications (e.g., poorly controlled chronic hypertension, preeclampsia, eclampsia, overt diabetes mellitus, or placenta previa),

postoperative complications such as postpartum hemorrhage or infection, mother-infant separation, or a known allergy to ginger.

A computer-generated randomization sequence using blocks of four was employed to assign participants to the intervention group or the placebo group. The randomization list was securely maintained in sealed, opaque, and non-transparent envelopes. To ensure blinding, a non-research nurse in the postpartum ward opened the envelope after the surgical procedure. Both the participants and the research team, including attending physicians and nurses, remained blind to the group assignments throughout the study.

The ginger powder dosage was set at 1,500 mg/day (KMP Brand, Kaewmungkornphaesaj Co., Ltd., Thailand), representing an increase from the 1,000 mg/day dose used in prior studies<sup>(7)</sup>. This adjustment was intended to enhance gastrointestinal motility during early oral feeding while ensuring maternal comfort by minimizing potential side effects. Both ginger and placebo capsules were manufactured under aseptic conditions by a licensed pharmacist and were identical in appearance and packaging.

The sweetened solution protocol was modeled after prior research demonstrating a significant increase in milk production among women undergoing emergency C-sections<sup>(15)</sup>. Specifically, a 200-mL serving was prepared by the hospital's nutrition and dietetics department. The solution consisted of 30 mL of red salacca-flavored syrup (Hale's Blue Boy) diluted with 170 mL of water. This preparation provides approximately 22.5–25 grams of simple carbohydrates, yielding an energy content of 90–110 kcal. This specific volume and caloric density have been shown to be well-tolerated postoperatively without increasing the risk of aspiration or nausea. Furthermore, the carbohydrates provide the essential metabolic energy to stimulate the gastrocolic reflex, mitigate postoperative insulin resistance, and support the energy-intensive process of lactogenesis<sup>(22-24)</sup>.

In the intervention group, at 6 hours postpartum (the standardized timing for transfer from the recovery

room to the postpartum ward), participants received an initial 200-mL serving of a sweetened clear solution along with a 500-mg ginger capsule administered orally. Subsequently, participants received ginger capsules three times daily (morning, afternoon, and evening, within 30 minutes after meals) for three days, until the assessment of breast milk volume at 72 hours postpartum.

In the placebo group, participants followed the same protocol, receiving the 200-mL sweetened clear solution alongside a 500-mg capsule containing fine brown sugar (Xongdur Brand, Xongdur Thai Organic Food Co., Ltd., Thailand) as a placebo.

To prevent dietary confounding, all participants were restricted to a standardized hospital diet, which was strictly screened to exclude ginger and other galactagogues (e.g., sweet basil or banana blossoms). Participants were instructed to avoid any outside supplementary foods or herbs during admission, with compliance monitored by the postpartum nursing staff.

All participants received standardized postpartum care, including 24-hour rooming-in and the initiation of breastfeeding within 2 hours post-delivery. Mothers were instructed to breastfeed for at least 20 minutes per session, 8-10 times per day, without routine infant formula supplementation. The dietary progression followed a systematic step from clear liquids to a soft diet and subsequently to a regular diet. Daily latch, audible swallowing, type of nipple, comfort, and hold (LATCH) scoring, neonatal weight tracking, and jaundice monitoring were performed for all participants.

The breast milk volume was measured at 72 hours postpartum. To ensure an objective and standardized measurement, a two-part pumping protocol was implemented. First, at 70 hours postpartum, participants breastfed their infants. Immediately afterwards, both breasts were fully emptied using a double-electric breast pump (Attitude Mom Little Plus Pro). A second pumping session was then performed two hours later, at 72 hours, to measure the final breast milk volume by 5-ml syringe.

The pumping process followed a standardized protocol: mode M3 was used initially for stimulation, followed by mode M4 for a thorough expression until milk flow ceased.

Secondary outcomes included the maternal perception of the OL and any adverse effects related to early feeding and ginger intervention. Following the methodology of established studies<sup>(15, 25)</sup>, OL was defined as the time when a mother first perceived specific symptoms, including breast fullness, tingling sensations, or visible milk flow/leakage<sup>(15, 26)</sup>. To enhance the reliability of these self-reports, participants were educated by the nursing staff to prioritize the observation of actual milk secretion as the primary indicator of OL. OL was recorded during the participants' hospital stay. For those who did not experience OL before discharge, daily follow-up telephone calls were conducted until OL occurred. Furthermore, adverse effects—such as gastric irritation, abdominal distension, or warm extremities—were monitored. Neonatal outcomes, including jaundice and excessive weight loss (defined as > 10% of birth weight<sup>(15, 27)</sup>), were also recorded.

Based on a pilot study of 30 participants, the sample size was calculated using the formula mentioned above. The mean breast milk volume was 24.66 mL with a standard deviation (SD) of 16.51 in the intervention group, while the control group had a mean of 13.8 mL with an SD of 10.06. To achieve 90% power with an alpha level of 0.05 and to account for a 10% dropout rate, a total of 84 participants (42 per group) was needed.

Statistical analyses were performed using R software version 4.4.1. The Shapiro-Wilk test was used to assess data normality. Continuous data were analyzed using the student's t-test or the Wilcoxon rank-sum test. Categorical data were analyzed using Pearson's chi-squared test or Fisher's exact test. The primary outcome was presented as a median with an interquartile range (IQR). The time to the onset of lactation was analyzed using Kaplan-Meier survival curves and the log-rank test. A p value of less than 0.05 was considered statistically significant. All

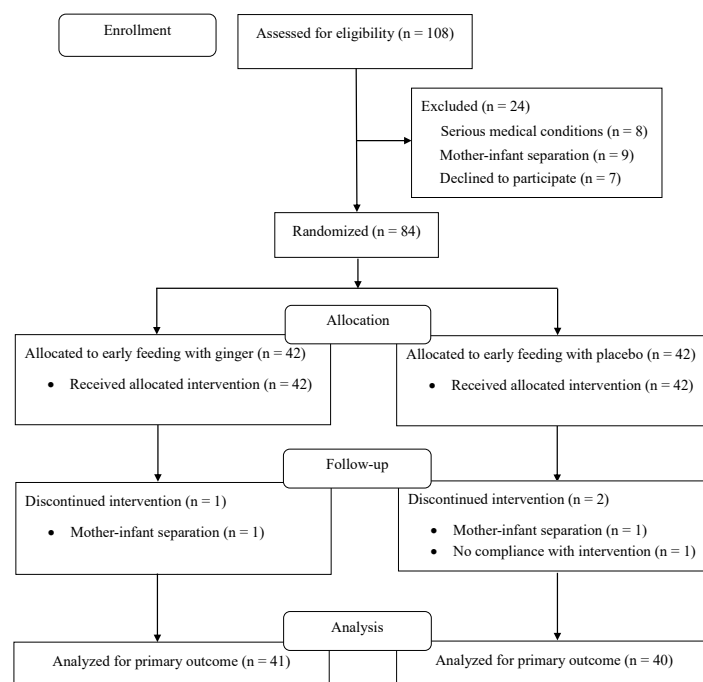
analyses were conducted using the intention-to-treat (ITT) principle.

## Results

This study included scheduled C-section parturient women, with a total of 108 participants assessed for eligibility. Of these, 24 were excluded: eight with serious medical conditions, nine due to mother-infant separation, and seven who declined to participate. As a result, 84 participants were randomized into two groups: the early feeding with ginger group (n = 42) and the early feeding alone group (n = 42).

After randomization, one participant from the early feeding with ginger group dropped out due to mother–infant separation. In the early feeding alone group, there were two participants who dropped out, one due to mother-infant separation and one due to non-compliance. Therefore, 41 participants in the early feeding with ginger group and 40 participants in the early feeding alone group were included in the final analysis, as illustrated in the CONSORT flow diagram (Fig. 1).

Baseline characteristics (Table 1), including maternal age, body mass index, gestational age, primiparity, indication for C-section, breastfeeding experience, type of surgical incision, estimated blood loss, neonatal birth weight, Apgar scores, and LATCH scores, were presented. There were no statistically significant differences between the two groups. The majority of participants in both groups were primiparous, with 23 women (56.1%) in the early feeding with ginger group and 23 women (57.5%) in the early feeding alone group. The most common indications for a cesarean section in both groups were cephalopelvic disproportion, followed by a history of previous C-section, breech presentation, oligohydramnios, low-lying placenta, and a history of poor obstetric outcomes. Two participants had an underlying disease. One participant with gestational diabetes mellitus was in the intervention group, and one participant with chronic hypertension was in the control group.



**Fig. 1.** CONSORT flow diagram.

**Table 1.** Baseline Characteristics.

| Demographic profiles                                | Early feeding with ginger<br>(n = 41) | Early feeding alone<br>(n = 40) | p value            |
|-----------------------------------------------------|---------------------------------------|---------------------------------|--------------------|
| Age (years), mean $\pm$ SD                          | 30.9 $\pm$ 5.3                        | 30.1 $\pm$ 3.7                  | 0.447 <sup>a</sup> |
| Body mass index (kg/m <sup>2</sup> ), mean $\pm$ SD | 28.7 $\pm$ 4                          | 27.6 $\pm$ 4                    | 0.193 <sup>a</sup> |
| Gestational age (weeks), median (IQR)               | 38 (38,39)                            | 38 (38,38.2)                    | 0.263 <sup>b</sup> |
| Primiparity, n (%)                                  | 23 (56.1)                             | 23 (57.5)                       | 1.000 <sup>c</sup> |
| Breastfeeding experience, n (%)                     | 17 (41.5)                             | 16 (40)                         | 1.000 <sup>c</sup> |
| C-section indication, n (%)                         |                                       |                                 | 0.677 <sup>d</sup> |
| Previous C-section                                  | 13 (31.7)                             | 17 (42.5)                       |                    |
| Cephalopelvic disproportion                         | 24 (58.6)                             | 18 (45.0)                       |                    |
| Breech presentation                                 | 2 (4.9)                               | 1 (2.5)                         |                    |
| Others                                              | 2 (4.9)                               | 4 (10)                          |                    |
| Type of surgical incision, n (%)                    |                                       |                                 | 0.482 <sup>d</sup> |
| Pfannenstiel                                        | 35 (85.4)                             | 37 (92.5)                       |                    |
| Low midline                                         | 6 (14.6)                              | 3 (7.5)                         |                    |
| Estimated blood loss (mL), median (IQR)             | 300 (300, 400)                        | 400 (300, 500)                  | 0.338 <sup>b</sup> |
| Birth body weight (grams), mean $\pm$ SD            | 3,204 $\pm$ 373.7                     | 3,151 $\pm$ 421.4               | 0.548 <sup>a</sup> |
| Apgar score, mean $\pm$ SD                          |                                       |                                 |                    |
| At 1 minute                                         | 8.2 $\pm$ 0.4                         | 8.2 $\pm$ 0.4                   | 0.757 <sup>a</sup> |
| At 5 minutes                                        | 9.1 $\pm$ 0.6                         | 9.2 $\pm$ 0.4                   | 0.493 <sup>a</sup> |
| LATCH score, median (IQR)                           |                                       |                                 |                    |
| At 24 hours                                         | 8 (8,8)                               | 8 (8,8)                         | 0.197 <sup>b</sup> |
| At 48 hours                                         | 8 (8,8)                               | 8 (8,8)                         | 0.328 <sup>b</sup> |
| At 72 hours                                         | 9 (9,9)                               | 9 (9,9)                         | 0.768 <sup>b</sup> |

SD: standard deviation, IQR: interquartile range, C-section: cesarean section, LATCH: latch, audible swallowing, type of nipple, comfort, and hold

<sup>a</sup> student's t-test, <sup>b</sup> Wilcoxon rank-sum test, <sup>c</sup> Pearson's Chi-squared test, <sup>d</sup> Fisher's exact test

The primary outcome of the study was breast milk volume at 72 hours postpartum (Table 2). The median breast milk volume was 20 mL (IQR 14, 35) in the early feeding with ginger group, compared to 10.5 mL (IQR 9, 15) in the early feeding alone group, demonstrating a statistically significant difference ( $p < 0.001$ ).

When categorized by parity, significant differences remained consistent across both

groups. Among primiparous participants, the median milk volume in the ginger group was 20 mL (IQR 13, 36.5), compared to 10 mL (IQR 8, 14.5) in the early feeding alone group ( $p < 0.001$ ). Similarly, for multiparous participants, the ginger group produced a median volume of 19.5 mL (IQR 15, 25.8), while the early feeding alone group produced 12 mL (IQR 10, 15,  $p = 0.009$ ).

**Table 2.** Breast milk volume at 72 h postpartum.

| Breast milk volume                    | Early feeding with ginger<br>(n = 41) | Early feeding alone<br>(n = 40) | p value            |
|---------------------------------------|---------------------------------------|---------------------------------|--------------------|
| At 72 h postpartum (mL), median (IQR) | 20 (14, 35)                           | 10.5 (9, 15)                    | $< 0.001^a$        |
| Primiparous (mL), median (IQR)        | 20 (13, 36.5)                         | 10 (8, 14.5)                    | $< 0.001^a$        |
| Multiparous (mL), median (IQR)        | 19.5 (15, 25.8)                       | 12 (10, 15)                     | 0.009 <sup>a</sup> |

IQR: Interquartile range, <sup>a</sup> Rank-sum test

SD: standard deviation, IQR: interquartile range

Secondary outcomes are presented in Table 3. The median time to the OL, based on maternal perception, was significantly shorter in the ginger group compared to the control group (59 hours vs 69 hours,  $p < 0.001$ ). The cumulative probability of maternal perception of OL is illustrated in Fig. 2. Delayed onset of lactation—defined as OL  $\geq$  72 hours<sup>(28, 29)</sup>—occurred in 4 participants (9.8%) in the ginger group and 10 participants (25%) in the control group, although this difference did not reach statistical significance. Regarding gastrointestinal outcomes, the

incidence of mild abdominal distention and upset stomach was lower in the ginger group (31.7%) compared to the control group (50.0%), although this difference was not statistically significant. No cases of severe bowel ileus were observed. In terms of safety, one participant in the ginger group reported warm extremities, which were not associated with any adverse clinical outcomes. Regarding neonatal outcomes, two cases of jaundice occurred exclusively in the control group, and no instances of excessive neonatal weight loss were reported in either group.

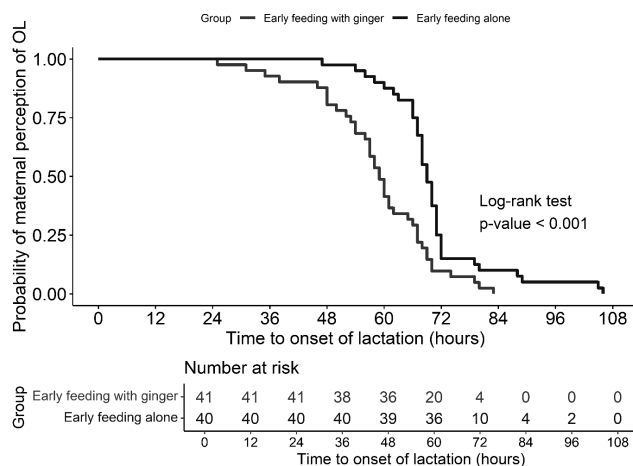
**Table 3.** Time to onset of lactation, side effects, and neonatal outcomes.

| Secondary outcomes                             | Early feeding with ginger<br>(n = 41) | Early feeding alone<br>(n = 40) | p value            |
|------------------------------------------------|---------------------------------------|---------------------------------|--------------------|
| Time to onset of lactation (h), median (95%CI) | 59 (57, 65)                           | 69 (68, 71)                     | $< 0.001^a$        |
| Delayed onset of lactation, n (%)              | 4 (9.8)                               | 10 (25)                         | 0.128 <sup>b</sup> |
| Side effects, n (%)                            |                                       |                                 |                    |
| Mild abdominal distention/upset stomach        | 13 (31.7)                             | 20 (50)                         | 0.147 <sup>b</sup> |
| Warm extremities                               | 1 (2.4)                               | 0 (0)                           | 1.000 <sup>c</sup> |
| Neonatal outcome, n (%)                        |                                       |                                 |                    |
| Neonatal jaundice                              | 0 (0)                                 | 2 (5)                           | 0.241 <sup>c</sup> |

CI: confidence interval

<sup>a</sup> Log-rank test, <sup>b</sup> Pearson's Chi-squared test, <sup>c</sup> Fisher's exact test

Delayed onset of lactation: onset of lactation  $\geq$  72 hours



**Fig. 2.** The Kaplan-Meier curves of the cumulative probability of maternal perception of onset of lactation.

## Discussion

This study is the first to investigate the combined effect of ginger supplementation and early oral feeding on breast milk volume in mothers following a scheduled C-section. A key strength of our study lied in the direct quantification of breast milk volume, providing a more objective and reliable measure than the subjective metrics used in several prior studies<sup>(15, 17, 18)</sup>. While previous research often relied solely on maternal perception of the OL—a tool for assessing lactogenesis II that can be prone to recall bias<sup>(25)</sup>—our approach aimed to improve precision and provide a stronger evidence base by measuring actual volumetric output.

Current study results showed that women who had a scheduled C-section and received early feeding with ginger produced significantly greater breast milk volume at 72 hours postpartum compared to those who received early feeding alone (20 mL [IQR 14, 35] vs 10.5 mL [IQR 9, 15],  $p < 0.001$ ). This finding was supported by a shorter median time to the OL in the ginger group (59 h vs 69 h,  $p < 0.001$ ). These results were consistent with a prior study conducted in women who had emergency cesarean sections<sup>(17)</sup>, which also found that OL was significantly shorter in the early feeding with ginger group (35.3 h) compared to the early feeding alone group (41.0 h) and the

conventional feeding group (50.5 h). However, the overall time to OL in our study was comparatively longer, likely due to the difference in settings. Scheduled C-sections are known to significantly delay lactation to a greater degree than emergency C-sections because they lack the hormonal signaling that occurs during labor, particularly prolactin and oxytocin, which are crucial for milk production and secretion<sup>(30, 31)</sup>.

Additionally, the supplementation of ginger in our early feeding protocol aligned with the study of Wang Nam Yen herbal tea, which utilized the same ginger dosage of 1.5 g per day<sup>(32)</sup>. That study demonstrated that this dosage could significantly stimulate breast milk production, showing a higher milk volume at 72 hours compared to the placebo ( $57.5 \pm 50.7$  vs.  $31.9 \pm 27.7$  mL,  $p = 0.03$ ), thereby confirming its efficacy as a galactagogue at this dose. However, the total milk volume in the Wang Nam Yen study was higher than in our findings, which can be explained by two main factors. First, their formulation contained four additional herbs (sappan wood, licorice, bael fruit, and jewel vine) that also stimulate milk production, likely creating a stronger synergistic effect. Second, while our study exclusively focused on scheduled C-sections, their study included emergency cases. As mentioned previously, mothers

in emergency cases may have experienced labor before surgery, triggering the hormonal surges necessary to stimulate higher initial milk production. The combined effect of early oral feeding and ginger supplementation on breast milk volume can be explained by two complementary mechanisms. First, early postoperative oral feeding—a practice supported by ERAS guidelines as safe and effective<sup>(5)</sup>—directly stimulates intestinal motility and shortens the duration of postoperative ileus. This improvement in gastrointestinal function enhances maternal physical comfort and reduces symptoms such as nausea and abdominal distention. By mitigating these physical stressors, early feeding creates a more favorable physiological environment, potentially reducing cortisol levels that could otherwise inhibit oxytocin release<sup>(33, 34)</sup>.

Second, ginger's known vasodilatory effects may provide a synergistic benefit by increasing systemic blood flow. Specifically, ginger can enhance circulation to the mammary glands, thereby promoting more efficient milk production<sup>(7)</sup>. The combination of these two mechanisms—one focused on improving maternal comfort and hormonal readiness, and the other on directly stimulating mammary gland function—likely contributed to the greater breast milk volume observed in this study.

Regarding our secondary outcome, although OL is a subjective measure based on maternal perception, it was maintained for two primary reasons. First, it ensures comparability with existing literature<sup>(14, 15, 18, 26)</sup>, allowing our findings to be integrated into the broader body of lactation research. Second, from a clinical utility perspective, maternal perception of OL is a practical and accessible indicator. In many real-world clinical settings where precise volumetric measurement tools are unavailable, OL serves as an essential tool for mothers and healthcare providers to easily monitor breastfeeding progress.

In the current study, delayed OL was observed in 9.8% of the ginger group and 25% of the early feeding alone group. These rates were notably lower

than those reported in prior research, which found delayed OL in 33.3% of women in China and 53.0% in the USA following C-sections<sup>(29)</sup>. The longest time to OL recorded in our study was 108 hours postpartum. Importantly, no cases of neonatal jaundice or excessive weight loss were observed, even among participants with delayed OL.

Early postoperative oral feeding helps to accelerate the return of bowel activity, and the addition of ginger appeared to further reduce gastrointestinal discomfort and abdominal distention in the present study. This effect is likely mediated by 6-gingerol, an active compound in ginger that has been previously shown to reduce nausea and accelerate the return of bowel function post-surgery<sup>(10)</sup>. The authors hypothesized that the observed effects may not have reached the same level of statistical significance as in prior research due to the lower dosage administered in this study (1.5 g/day) compared to the higher dose (3 g/day) used in other trials, suggesting a potential dose-dependent effect. A minor side effect of warm extremities was reported by one participant in the ginger group. This observation was consistent with the known hyperthermic effect of ginger, which can induce vasodilation in the peripheral skin<sup>(35)</sup>. However, this finding was not statistically significant, and the symptom did not interfere with the patient's comfort, likely due to the low dosage of ginger administered in this study.

A major strength of this study is its randomized, double-blind, placebo-controlled design, which ensures high internal validity. We used data triangulation to validate subjective maternal reports with objective breast milk volume, measured precisely after total breast emptying. This rigorous approach provided a more accurate assessment of milk production than self-reporting alone.

However, some limitations must be acknowledged. First, individual physiological variations in the rate of breast milk production could not be fully controlled, despite the use of randomization. Second, this study was not specifically designed for a subgroup analysis based on parity. Therefore, the

data for primiparous and multiparous participants are provided as descriptive observations to show the overall trend of the intervention's effect, rather than for formal statistical comparison.

Future research should explore this intervention in high-risk pregnancies and mothers of preterm infants. Additionally, investigating various dosages could identify a dose-dependent response, while further analysis of the interaction between parity and ginger's efficacy would help tailor clinical outcomes for different maternal needs.

## Conclusion

Oral ginger supplementation combined with early feeding significantly increased breast milk volume and shortened the OL in women undergoing scheduled C-sections, with no serious adverse events reported. These findings suggest that ginger is a safe and effective adjunct to early postoperative feeding; however, further studies with larger, specifically powered samples are encouraged to confirm these effects across different maternal characteristics.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## OBSTETRICS

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# Effectiveness of Topical 2% Lidocaine Gel for Post-episiotomy Pain Relief: A randomized, Double-blind trial

Nattakrid Sintrakulchai, M.D.\*,  
Chokchai Chotboon, M.D.\*,  
Purinat Jaitham, M.D.\*,  
Metha Songthamwat, M.D.,Ph.D.\*

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

### ABSTRACT

**Objectives:** To evaluate the effectiveness and safety of topical 2% lidocaine gel versus a placebo for post-episiotomy analgesia, assessed using the numeric rating scale (NRS) pain scores at 6, 12, and 24 hours postpartum.

**Materials and Methods:** This randomized, double-blind, placebo-controlled trial was conducted at a tertiary care hospital in Thailand. A total of 184 women who underwent vaginal delivery with episiotomy were randomized to receive topical 2% lidocaine gel (n = 92) or placebo gel (n = 92), applied as a thin layer to the perineal wound every 4 hours for 12 hours post-repair. Pain was assessed with the NRS at 6, 12, and 24 hours by blinded assessors. Secondary outcomes included rescue-analgesic use within 24 hours, lochia pad count, perineal wound events (hematoma, dehiscence, infection), adverse events and length of hospital stay.

**Results:** Mean NRS pain scores at 6, 12, and 24 hours were not different between groups: mean difference -0.11 (95% confidence interval (CI) -0.5, 0.28), -0.21 (-0.56, 0.15), and -0.21 (-0.51, 0.10), respectively. Rescue-analgesic use was similar in both groups (46.7% vs 56.5%; relative risk (RR) 0.83, 95% CI 0.62, 1.10). No drug-related adverse events or maternal complications were observed. The lidocaine group had a significantly higher lochia pad count ( $p < 0.001$ ), whereas the length of hospital stay was significantly shorter than in the placebo group ( $p = 0.019$ ).

**Conclusion:** Topical 2% lidocaine gel did not provide a statistically significant reduction in post-episiotomy perineal pain during the first 24 hours compared with placebo. Therefore, it should not be recommended as a first-line analgesic in this setting.

**Keywords:** episiotomy wound, postpartum perineal pain, lidocaine gel, topical anesthetics, randomized controlled trial, numerical rating scale.

**Correspondence to:** Metha Songthamwat, M.D., Ph.D., Department of Obstetrics and Gynecology, Udon Thani Hospital, Udon Thani 41000, Thailand. E-mail: [udonhome@yahoo.com](mailto:udonhome@yahoo.com)

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## ประสิทธิผลของเจลลิโดเคนร้อยละ 2 ชนิดใช้เฉพาะที่ในการบรรเทาปวดหลังการตัดฝีเย็บ: การทดลองแบบสุ่ม ปกปิดสองทาง

ณัฐกฤษฏี สินตระกูลชัย, โชคชัย โชติบุรณ์, ภูริณัฐ ใจธรรม, เมธา ทรงธรรมวัฒน์

### บทคัดย่อ

**วัตถุประสงค์:** ประเมินประสิทธิผลและความปลอดภัยของเจลลิโดเคนร้อยละ 2 ชนิดใช้เฉพาะที่เมื่อเทียบกับยาหลอกในการบรรเทาปวดหลังการตัดฝีเย็บ โดยวัดด้วยคะแนนความปวดแบบตัวเลข (NRS) ที่ 6, 12 และ 24 ชั่วโมงหลังคลอด

**วัสดุและวิธีการ:** การทดลองแบบสุ่ม ปกปิดสองทาง และมีกลุ่มควบคุมด้วยยาหลอก ดำเนินการที่โรงพยาบาลตติยภูมิในประเทศไทย สตรีที่คลอดทางช่องคลอดร่วมกับการตัดฝีเย็บจำนวน 184 ราย ถูกสุ่มให้ได้รับเจลลิโดเคนร้อยละ 2 ( $n = 92$ ) หรือเจลยาหลอก ( $n = 92$ ) ทาบาง ๆ บริเวณแผลฝีเย็บ ทุก 4 ชั่วโมง นาน 12 ชั่วโมง หลังเย็บซ่อม ประเมินความปวดด้วย NRS ที่ 6, 12 และ 24 ชั่วโมง โดยผู้ประเมินที่ไม่ทราบการจัดกลุ่ม ผลลัพธ์รองได้แก่ การใช้ยาแก้ปวดเพิ่มเติมภายใน 24 ชั่วโมง จำนวนผ้าอนามัยที่ใส่รองน้ำคาวปลา ภาวะแทรกซ้อนที่แผลฝีเย็บ (เลือดคั่ง แผลแยก การติดเชื้อ) อาการไม่พึงประสงค์จากยา และระยะเวลาการนอนโรงพยาบาล

**ผลการศึกษา:** ค่าคะแนนความปวดเฉลี่ยแบบ NRS ที่ 6, 12 และ 24 ชั่วโมงไม่มีความแตกต่างกันระหว่างกลุ่ม: ผลต่างค่าเฉลี่ย -0.11 (95% Confidence interval (CI) -0.50, 0.28), -0.21 (95% CI -0.56, 0.15), และ -0.21 (95% CI -0.51, 0.10) ตามลำดับ อัตราการใช้ยาแก้ปวดเพิ่มเติมใกล้เคียงกัน (ร้อยละ 46.7 เปรียบเทียบกับ 56.5; relative risk [RR] 0.83, 95% CI 0.62, 1.10) ไม่พบอาการไม่พึงประสงค์ที่เกี่ยวข้องกับยาหรือภาวะแทรกซ้อนในมารดา กลุ่มลิโดเคนมีจำนวนผ้าอนามัยที่ใส่รองน้ำคาวปลามากกว่าอย่างมีนัยสำคัญ ( $p < 0.001$ ) ขณะที่ระยะเวลาการนอนโรงพยาบาลสั้นกว่ากลุ่มยาหลอก ( $p = 0.019$ )

**สรุป:** เจลลิโดเคนร้อยละ 2 ชนิดใช้เฉพาะที่ ไม่ทำให้ความปวดหลังการตัดฝีเย็บลดลงอย่างมีนัยสำคัญในช่วง 24 ชั่วโมงแรก เมื่อเทียบกับยาหลอก จึงไม่ควรแนะนำเป็นยาแก้ปวดหลัก

**คำสำคัญ:** แผลฝีเย็บ, ความปวดฝีเย็บหลังคลอด, เจลลิโดเคน; ยาชาเฉพาะที่, การทดลองแบบสุ่มมีกลุ่มควบคุม, คะแนนความปวดแบบตัวเลข

## Introduction

Episiotomy is a common procedure performed during vaginal delivery. The incision can be made either in a midline or mediolateral direction<sup>(1)</sup>. Primigravid women have a higher likelihood of undergoing episiotomy compared with women who have previously delivered vaginally<sup>(2)</sup>. Although global practice has shifted toward restrictive rather than routine use<sup>(3)</sup>, the high prevalence of episiotomy and subsequent perineal pain remains a significant challenge in Thai obstetric care. Recent studies continue to highlight that postpartum perineal pain is a common and distressing experience, with a substantial number of women reporting moderate to severe pain levels following the procedure<sup>(5)</sup>.

The pathogenesis of post-episiotomy pain involves acute mechanical trauma to the perineal tissues and a subsequent inflammatory cascade. The surgical incision directly stimulates nociceptors and may cause peripheral nerve damage, followed by the release of inflammatory mediators, such as prostaglandins and bradykinin, which sensitize nerve endings and lower the pain threshold at the site of injury<sup>(5,6)</sup>. Postpartum perineal pain following episiotomy is common. Severe pain in the early postpartum period can contribute to maternal fatigue and psychological stress, which may interfere with the mother–infant relationship and the ability to perform routine activities such as sitting, walking, defecation, breastfeeding, and caring for the newborn<sup>(7–9)</sup>.

Various methods have been employed to reduce post-episiotomy perineal pain, including the application of heat or cold, the use of oral analgesics, and the administration of local anesthetics. However, each approach has advantages and limitations. For example, oral analgesics may cause gastrointestinal side effects or maternal drowsiness, whereas the application of heat or cold may provide only modest, short-lived relief<sup>(10,11)</sup>.

Lidocaine is a local anesthetic that acts by inhibiting voltage-gated sodium channels on neuronal cell membranes, thereby blocking the transmission of nerve impulses to the brain and reducing pain

perception at the site of application<sup>(12)</sup>. Through this mechanism, it provides localized analgesia without affecting the central nervous system. Small randomized trials have evaluated topical anesthetics for post-episiotomy pain, including 2% lidocaine gel and lidocaine ointments/sprays, indicating possible benefit but heterogeneity in formulation, dosing, and timing, as well as limited safety reporting<sup>(13–17)</sup>. Therefore, this double-blind randomized controlled trial aimed to evaluate the effectiveness of 2% lidocaine gel for reducing post-episiotomy perineal pain.

## Materials and Methods

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at Udon Thani Hospital, a tertiary care center in Thailand. The study protocol was approved by the Udon Thani Hospital Ethics Committee in Human Research (approval no.4/2568) and was prospectively registered with the Thai Clinical Trials Registry (TCTR20250310001).

The inclusion criteria were postpartum women with singleton pregnancies who underwent vaginal delivery with episiotomy at Udon Thani Hospital, with a gestational age between 37 and 41 weeks, aged 18 years or older, and who provided written informed consent. The exclusion criteria were (i) known hypersensitivity/allergy to lidocaine, other amide-type local anesthetics or gel excipients; (ii) obstetric anal sphincter injury (third- or fourth-degree tear) or perineal hematoma; (iii) postpartum hemorrhage (more than 500 cc); (iv) admission to the intensive care unit or endotracheal intubation after delivery.

Postpartum women who had a vaginal delivery with episiotomy were screened for eligibility. Eligible women received detailed study information in the labor room and, if willing, provided written informed consent before any study procedures. Eligible women were randomized into two groups. Group 1 received 5 mL of topical 2% lidocaine gel applied to the episiotomy wound every 4 hours for 12 hours (four scheduled applications at 4, 8, 12, and 16 hours postpartum). Group 2 received 5 mL of matching placebo gel on the same schedule.

The first application was performed 4 hours after delivery, following the completion of the episiotomy wound repair, by trained nurses, using a standardized technique. The 5 mL dose was uniformly applied as a continuous coating, approximately 1–2 mm in thickness, sufficient to cover the entire length of the incision to both the external perineal skin and the internal vaginal mucosal edge of the episiotomy incision, after gentle cleansing and drying of the area. Both groups received identical standard intrapartum and postpartum care. All participants underwent a mediolateral episiotomy; local anesthetic infiltration with 1% lidocaine (Xylocaine®) was performed prior to the incision. Episiotomies were repaired with chromic catgut using a standardized three-layer technique: continuous non-locking sutures for the vaginal mucosa and interrupted sutures for the perineal musculature and skin to ensure anatomical apposition.

Pain was assessed using the numerical rating scale (NRS; 0–10, higher scores = more pain) at 6, 12, and 24 hours postpartum by blinded assessors. Additional outcomes included the proportion of participants requiring rescue analgesia and the cumulative 24-hour dose (paracetamol, non-steroidal anti-inflammatory drugs, or opioids), length of hospital stay, and episiotomy wound infection. Lochia pad count (number of sanitary pads used) was recorded as a control variable.

Participants were scheduled for a 6-week postpartum follow-up in the clinic or, if unavailable, via telephone interview to assess for episiotomy-wound complications (dehiscence or infection). All data were recorded and subsequently analyzed.

Randomization (1:1) used a computer-generated sequence, and allocation concealment was maintained with sequentially numbered, sealed, opaque envelopes. At enrollment, authorized study staff opened the next envelope to obtain the study code and dispensed the corresponding gel. A hospital pharmacist prepared the 2% lidocaine gel and matching placebo gel (K-Y gel) to be identical in appearance and packaging, labeled only with a study

code. Participants, care providers, and outcome assessors were blinded to group assignment. Blinding was maintained throughout the study; emergency unblinding was permitted only for patient safety.

The primary outcome of this study was the comparison of mean  $\pm$  standard deviation (SD) NRS pain scores between the two groups at 6, 12, and 24 hours postpartum. The secondary outcomes included the proportion of participants requiring rescue analgesia and the cumulative 24-hour dose of analgesics (paracetamol, nonsteroidal anti-inflammatory drugs, or opioids), length of hospital stay, and episiotomy wound infection. Additionally, adverse events related to topical application (stinging/burning, pruritus, erythema, edema, and dermatitis) and systemic lidocaine-related symptoms (dizziness, perioral numbness, tinnitus, metallic taste, and palpitations), as well as allergic reactions and serious adverse events, were recorded until discharge.

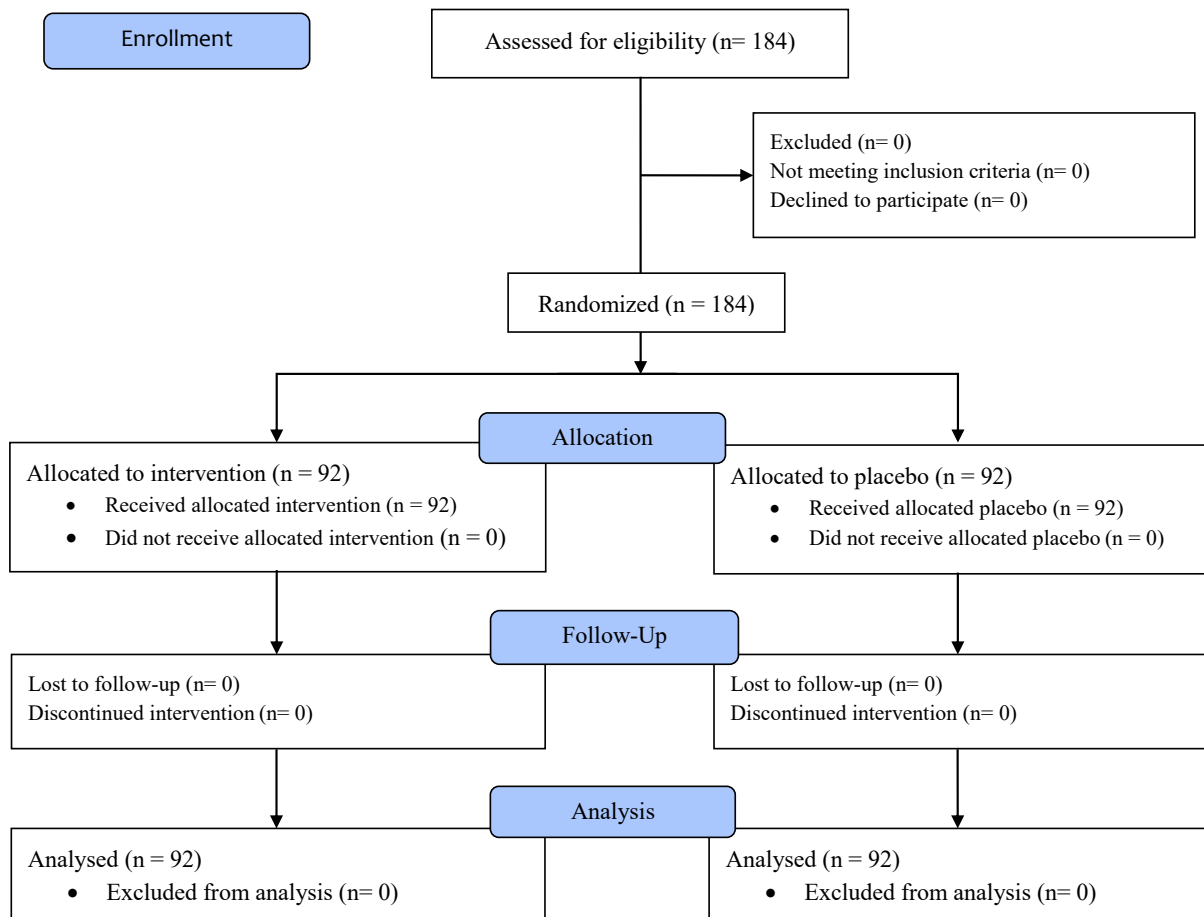
Sample size was calculated using the N4Studies application (18-20) for a two-sided comparison of independent means in a randomized controlled trial with 1:1 allocation. Estimates were taken from Abedzadeh et al(13): mean  $\pm$ SD NRS 12 hours postpartum of  $2.63 \pm 2.01$  in the intervention group and  $3.60 \pm 2.40$  in the control group. With  $\alpha = 0.05$ , 80% power, and an anticipated 10% dropout rate, the required sample size was 92 participants per group (total  $n = 184$ ).

Statistical analyses were performed using Stata version 13 (StataCorp, College Station, TX). Continuous data were reported as mean  $\pm$  SD, and categorical data as frequencies (percentages). Independent samples t-test was used to compare continuous variables; results were presented as mean differences with 95% confidence intervals (CI). For categorical variables, chi-square or Fisher's exact tests were applied, and relative risks (RR) with 95% CI were estimated using a generalized linear model. All tests were two-sided, with  $p < 0.05$  considered statistically significant. All analyses followed the intention-to-treat principle.

## Results

The trial enrolled a total of 184 women, with 92 participants allocated to receive 2% lidocaine gel and 92 allocated to the placebo group. As demonstrated in the CONSORT flow diagram in Fig. 1, all 184 randomized participants completed the study protocols and were included in the final intention-to-treat analysis. Baseline maternal and neonatal characteristics were comparable between the two study arms as demonstrated in Table 1. All participants underwent a mediolateral episiotomy and sustained a second-degree perineal tear. The mean maternal age was  $26.8 \pm 5.64$  years in the lidocaine group and  $27.22 \pm 4.91$  years in the

placebo group<sup>(4)</sup>. The distribution of primigravid women (50.0% vs 41.3%,  $p = 0.236$ ) and the mean gestational age at delivery ( $38.65 \pm 1.08$  vs  $38.65 \pm 1.03$  weeks) showed no statistically significant differences<sup>(5)</sup>. Neonatal outcomes, including the distribution of male infants (51.1% vs 46.7%) and birth weight ( $3,055.76 \pm 319.71$  vs  $3,131.58 \pm 313.35$  grams), were also balanced between the groups. Additionally, the estimated blood loss was similar between the intervention and placebo groups ( $135 \pm 66.01$  mL vs  $147.28 \pm 71.38$  mL)<sup>(7)</sup>. Furthermore, no cases of multiple gestations or fetal growth restriction were enrolled in the study population<sup>(8)</sup>.



**Fig. 1.** CONSORT flow diagram of the randomized, double-blind, placebo-controlled trial assessing topical 2% lidocaine gel for post-episiotomy analgesia in 184 postpartum women, demonstrating the progression from enrollment to final analysis.

**Table 1.** Comparison of baseline maternal and neonatal characteristics between the topical 2% lidocaine gel and placebo groups.

| Variable                                           | Intervention (n = 92) | Placebo (n = 92)  | p value* |
|----------------------------------------------------|-----------------------|-------------------|----------|
| Age (years)                                        | 26.8 ± 5.64           | 27.22 ± 4.91      | 0.636    |
| Primigravida                                       | 46 (50.00%)           | 38 (41.30%)       | 0.236    |
| Previous abortion                                  | 12 (13.04%)           | 13 (14.13%)       | 0.830    |
| Gestational age (weeks)                            | 38.65 ± 1.08          | 38.65 ± 1.03      | 1.000    |
| Underlying disease                                 |                       |                   |          |
| Diabetes mellitus                                  | 8 (8.70%)             | 6 (6.52%)         | 0.578    |
| Others                                             | 4 (4.3%)              | 5 (5.43%)         | 1.000    |
| Smoking                                            | 2 (2.17%)             | 1 (1.09%)         | 1.000    |
| Alcohol use                                        | 2 (2.17%)             | 0 (0%)            | 0.497    |
| History of methamphetamine use                     | 5 (5.43%)             | 4 (4.35%)         | 1.000    |
| Pre-pregnancy body mass index (kg/m <sup>2</sup> ) | 24.49 ± 5.59          | 24.48 ± 5.31      | 0.982    |
| Estimated blood loss (mL)                          | 135 ± 66.01           | 147.28 ± 71.38    | 0.253    |
| Male baby                                          | 47 (51.09%)           | 43 (46.74%)       | 0.555    |
| Birth weight (grams)                               | 3,055.76 ± 319.71     | 3,131.58 ± 313.35 | 0.106    |

Data are presented as mean ± standard deviation or n (%).

\* p values from Pearson's chi-square or Fisher's exact tests for categorical variables and independent samples t-test for continuous variables.

The primary outcome is summarized in Table 2. Pain scores and analgesic requirements regarding the primary outcome, the mean NRS pain scores were numerically lower in the lidocaine group at all assessment points; however, these differences were not statistically significant. Specifically, at 6, 12, and 24 hours postpartum, the mean differences were -0.11

(95% CI -0.50, 0.28), -0.21 (-0.56, 0.15), and -0.21 (-0.51, 0.10), respectively (Table 2). In alignment with these findings, the requirement for rescue analgesia within the first 24 hours was comparable between groups, with 46.7% of women in the lidocaine group and 56.5% in the placebo group requiring additional pain medication (RR 0.83, 95% CI 0.62, 1.10).

**Table 2.** Comparison of postpartum episiotomy wound pain scores (NRS) and rescue analgesic requirements between women receiving topical 2% lidocaine gel (n = 92) and placebo (n = 92).

| Variable                        | Intervention (n = 92) | Placebo (n = 92) | Effect estimate (95% CI)                       |
|---------------------------------|-----------------------|------------------|------------------------------------------------|
| Pain score at 6 hours           | 2.69 ± 1.24           | 2.79 ± 1.42      | Mean difference (95% CI) - 0.11 (- 0.50, 0.28) |
| Pain score at 12 hours          | 2.04 ± 1.31           | 2.25 ± 1.14      | Mean difference (95% CI) - 0.21 (- 0.56, 0.15) |
| Pain score at 24 hours          | 1.50 ± 1.08           | 1.71 ± 1.02      | Mean difference (95% CI) -0.21 (-0.51, 0.10)   |
| Additional pain control needed* | 43 (46.74%)           | 52 (56.52%)      | Risk ratio 0.83 (0.62, 1.10)                   |
| Paracetamol                     |                       |                  |                                                |
| 1 tablet (500 mg)               | 41 (44.6%)            | 52 (56.5%)       |                                                |
| 2 tablets (1,000 mg)            | 1 (1.1%)              | 0 (0%)           |                                                |
| Ibuprofen                       |                       |                  |                                                |
| 1 tablet (400 mg)               | 2 (2.2%)              | 3 (3.3%)         |                                                |
| Lochia pad use, pads/day,       | 3.66 ± 0.96           | 3.11 ± 0.86      | Mean difference (95% CI) 0.54 (0.28 to 0.81)   |
| Hospital stays                  |                       |                  | Risk ratio 0.33 (0.15 to 0.75)                 |
| 2 days                          | 85 (92.39%)           | 71 (77.17%)      |                                                |
| > 3 days                        | 7 (7.60%)             | 21 (22.82%)      |                                                |

\*Some patients received more than one medication.

Data are presented as mean ± standard deviation or n (%).

CI: confidence interval

For the secondary outcomes, safety assessments revealed no local application-site adverse events, such as erythema or pruritus, and no systemic lidocaine-related symptoms were reported in either group. Similarly, no systemic lidocaine-related adverse events, such as dizziness, perioral numbness, tinnitus, or palpitations, were reported. At the six-week postpartum follow-up, the incidence of episiotomy-wound complications, specifically dehiscence or infection, was zero in both the intervention and placebo groups.

The mean number of lochia pads used per day was significantly higher in the lidocaine group at  $3.66 \pm 0.96$  pads compared with  $3.11 \pm 0.86$  in the placebo group ( $p < 0.001$ ). Conversely, the length of hospital stay was significantly shorter in the intervention group compared with the placebo group. Specifically, 92.4% of participants in the lidocaine group were discharged within two days, whereas 77.2% of those in the placebo group achieved discharge within the same timeframe. Although a higher proportion of women in the placebo group required hospitalization for three days or longer, these delayed discharges were primarily attributed to neonatal indications, such as neonatal jaundice, rather than maternal factors.

## Discussion

In this randomized, double-blind, placebo-controlled trial, topical 2% lidocaine gel did not reduce post-episiotomy perineal pain compared with placebo. Mean NRS scores at 6, 12, and 24 hours were numerically lower in the lidocaine group but not statistically significant. Rescue-analgesic use (paracetamol, ibuprofen) was similar between groups. No local or systemic lidocaine-related adverse events were recorded, and no episiotomy-wound infection or dehiscence was detected at 6-week follow-up. Collectively, these findings suggested that post-repair application of 2% lidocaine gel did not provide a clinically meaningful analgesic advantage over placebo in the first 24 hours postpartum in this setting. Compared with the Iranian trial by Abedzadeh et al (2011), which showed that 2% lidocaine gel significantly

reduced mean pain scores at 12 hours ( $2.63 \pm 2.01$  vs  $3.60 \pm 2.40$  in the control group) and lowered the need for additional analgesics (8% vs 20%)<sup>(13)</sup>.

Similarly, a Thai randomized trial by Suwannapab et al (2025) reported that 10% lidocaine spray significantly reduced perineal wound pain at 24 and 48 hours after spontaneous vaginal birth with first-second degree perineal tears with mean difference pain score 1.20-1.40<sup>(4)</sup>. Trials using lidocaine-prilocaine combinations, such as Moradi (2019) and Abbas (2020) studies also found greater effectiveness than systemic or injectable comparators<sup>(16, 17)</sup>. The current study did not demonstrate these effects. Such discrepancies may reflect specific methodological variations, including the lower concentration (2%) compared with the 10% formulation used by Suwannapab et al. Additionally, the timing of the first application at four hours post-repair and the high rate of rescue-analgesic use (approximately 50%) in this study may have masked the gel's individual analgesic benefit, especially when compared with trials reporting significantly lower supplemental analgesic requirements.

Furthermore, the management of postpartum perineal pain in Thailand often involves systemic oral analgesics. Harasai et al (2020) demonstrated that a single dose of 400 mg ibuprofen combined with 1,000 mg acetaminophen provided significantly better pain relief than acetaminophen alone, particularly within the first two hours postpartum<sup>(21)</sup>. In the present study, although participants had access to rescue analgesics like paracetamol and ibuprofen, the addition of topical 2% lidocaine gel did not provide an additive benefit. This suggested that for early postpartum pain, potent systemic oral combinations might be more effective than the low-concentration topical gel used in the present trial.

Regarding the timing and formulation of topical anesthetics, Wongvivattanakarn et al (2025) recently reported that lidocaine-prilocaine cream (EMLA®), when used in conjunction with lidocaine injection, significantly reduced pain during the episiotomy repair process<sup>(22)</sup>. However, they noted that the analgesic

effect diminished by one hour after the repair. This observation aligned with the current findings, where 2% lidocaine gel applied four hours after the repair did not result in a statistically significant reduction in pain scores during the 24-hour postpartum period. These collective findings imply that while topical anesthetics are beneficial for procedural pain during suturing, their role in sustained postpartum pain relief may be limited by their concentration and duration of action.

Our findings are consistent with Delaram et al (2016), who compared 2% lidocaine cream with mefenamic acid after mediolateral episiotomy and reported no significant difference in pain reduction at 6, 12, or 24 hours<sup>(15)</sup>. These data suggested that topical lidocaine may offer analgesia comparable to standard regimens but not superior in the early postpartum period. Importantly, the current study also supported a favorable safety profile of lidocaine gel with no complications such as allergy, infection, or wound problems.

In this study, the number of lochia pads used per day was significantly higher in the lidocaine gel group compared to the placebo group. However, this observation likely represented an incidental finding rather than a true pharmacologic effect of the medication. To our knowledge, no prior study has directly linked topical lidocaine, including gel formulations, to increased postpartum lochia or bleeding. A pharmacokinetic report noted a single instance of slight vaginal bleeding 30–48 hours after vaginal lidocaine gel, but this occurred in a different context and did not establish causation for episiotomy wounds<sup>(23)</sup>. A systematic review of normal lochia patterns highlights the wide variability in both amount and duration of lochia, with methods of assessment ranging from pad weight to subjective self-report, and no standardized definition of what constitutes excessive lochia<sup>(24)</sup>. Given this inherent variability, the current finding may reflect measurement variation. Nevertheless, the observation should be interpreted with caution, and future studies using validated and objective measures of lochia are warranted to clarify

whether this association is real or incidental.

The clinical implication of this study was that topical 2% lidocaine gel did not provide a clinically meaningful reduction in post-episiotomy perineal pain during the first 24 hours compared with placebo. Therefore, it should not be recommended as a first-line analgesic in this setting. Future research should evaluate alternative topical formulations and strengths or multimodal approaches to postpartum perineal pain management, including larger multicenter trials to better define the role of lidocaine gel in postpartum care.

This study had several strengths. The randomized, double-blind, placebo-controlled design reduced the risk of bias, and the sample size was sufficient for between-group comparisons. At the same time, several limitations should be noted. First, this was a single-center study, which may limit generalizability to other settings. Second, while the NRS is a standardized tool, it relies on self-reported data, which is subjective and influenced by individual variability in pain perception. Third, treatment adherence was not quantified (exact amount applied, coverage of internal/external wound edges, contact time) may have technique-related variability. Fourth, rescue-analgesic policies were pragmatic and participant-dependent which could affect the assessment of pain. Fifth, all participants underwent a mediolateral episiotomy and had a second-degree perineal tear. Sixth, lochia was measured by pad counts rather than objective quantification. Seven, the volume of lidocaine administered by injection was adjusted according to the characteristics and size of the episiotomy wound and was not considered part of the study intervention; therefore, the exact amount used in each participant was not recorded.

## Conclusion

This randomized, double-blind, placebo-controlled trial demonstrated that topical 2% lidocaine gel did not provide a clinically meaningful reduction in post-episiotomy perineal pain during the first 24 hours compared with placebo. Throughout the first

24 hours postpartum, both mean NRS pain scores and the requirements for rescue analgesia remained comparable between the intervention and placebo groups. Consequently, topical 2% lidocaine gel should not be recommended as a first-line analgesic for perineal pain relief in this clinical setting.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

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# Efficacy of Preoperative Intravenous Tranexamic Acid to Reduce Blood Loss in Difficult Abdominal Hysterectomy for Benign Gynecological Disease: A randomized double-blind placebo-controlled trial

Jinjuta Jindaluang, M.D.\*,  
Jesada Wutitamasuk, M.D.\*,  
Thumwadee Tangsiriwatthana, M.D.\*

\* Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand

### ABSTRACT

**Objectives:** To determine the efficacy of tranexamic acid (TXA) in reducing intraoperative blood loss in difficult abdominal hysterectomy for benign gynecological disease.

**Materials and Methods:** A double-blind randomized controlled trial was conducted. Women who were at risk of a difficult abdominal hysterectomy for benign gynecological disease, with or without adnexal surgery, were included. The participants were randomly assigned into two groups, comprising an intervention group who received intravenous TXA 10mg/kg (diluted with normal saline up to 100 ml), and a control group who received 100 ml of normal saline 15 minutes before skin incision.

**Results:** Ninety-two eligible participants were randomly allocated into the intervention group (n = 46) and control groups (n = 46) between September 2024 and July 2025. Intraoperative measurement of blood loss was comparable between the TXA group and control group (median [interquartile range]: 239 [104–384] vs 280 [187–400] mL,  $p = 0.24$ ), and the incidence of blood loss exceeding 500 mL did not differ significantly between the groups (11.1% vs 22.2%,  $p = 0.26$ ). There were no statistically significant differences, including changes in hemoglobin levels and blood transfusion requirements. Additional perioperative TXA in the TXA group was significantly lower than in the control group (4.4% vs 22.2%,  $p = 0.03$ ). No serious adverse effects were observed.

**Conclusion:** Preoperative intravenous TXA did not reduce blood loss in cases of difficult abdominal hysterectomy for benign gynecological disease.

**Keywords:** tranexamic acid, difficult hysterectomy, bleeding prophylaxis.

**Correspondence to:** Jinjuta Jindaluang, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. E-mail: [nujinju@gmail.com](mailto:nujinju@gmail.com)

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## ประสิทธิภาพของยาทรานแซมิกเอซิด (TXA) แบบฉีดทางหลอดเลือดก่อนการผ่าตัดเพื่อลดการเสียเลือดขณะผ่าตัดมดลูกแบบเปิดหน้าท้องในสตรีที่ไม่ใช่มะเร็งกลุ่มที่ผ่าตัดยาก : การทดลองแบบสุ่มที่มีกลุ่มควบคุม

จินต์จุฑา จินดาหลวง, เจษฎา วุฒิธรรมสุข, ทูมวดี ตังศิริวัฒนา

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาประสิทธิภาพของการให้ยาทรานแซมิกเอซิด ก่อนผ่าตัดมดลูกแบบเปิดหน้าท้องชนิดที่ไม่ใช่มะเร็งเพื่อลดการเสียเลือดระหว่างผ่าตัดในสตรีที่มีความเสี่ยงสูงต่อการผ่าตัดยาก

**วัสดุและวิธีการ:** เป็นการศึกษาแบบสุ่มชนิดปกปิดข้อมูลสองทาง โดยศึกษาในอาสาสมัครที่ต้องผ่าตัดมดลูกทางหน้าท้องและมีความเสี่ยงต่อการผ่าตัดยาก ได้รับการแบ่งสุ่มเป็นสองกลุ่ม คือกลุ่มทำการทดลองจะได้รับยาทรานแซมิกเอซิดปริมาณ 10 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม (ผสมละลายในนอร์มอลซาลินจ์จนครบ 100 มิลลิลิตร) ทางหลอดเลือดดำก่อนลงมีดผ่าตัด 15 นาที และกลุ่มควบคุมได้รับ นอร์มอลซาลินจ์ปริมาณ 100 มิลลิลิตร ทางหลอดเลือดดำที่ 15 นาที ก่อนลงมีดผ่าตัดเช่นเดียวกัน

**ผลการศึกษา:** อาสาสมัครจำนวน 92 ราย ระหว่างเดือนกันยายน พ.ศ.2567 ถึง กรกฎาคม พ.ศ.2568 แบ่งสุ่มเป็นกลุ่มที่ได้รับยาทรานแซมิกเอซิดจำนวน 46 รายและกลุ่มควบคุมจำนวน 46 ราย ปริมาณการสูญเสียเลือดระหว่างผ่าตัดในกลุ่มทรานแซมิกเอซิดและกลุ่มควบคุมไม่มีความแตกต่างกันอย่างมีนัยสำคัญ (ค่ามัธยฐาน 239 มิลลิลิตร [พิสัยระหว่างควอไทล์ 104, 384] และ 280 มิลลิลิตร [187, 400] ตามลำดับ,  $p = 0.24$ ) เช่นเดียวกับจำนวนผู้ที่เสียเลือดมากกว่า 500 มิลลิลิตร ซึ่งพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างสองกลุ่ม (ร้อยละ 11.1 และร้อยละ 22.2,  $p = 0.26$ ) ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติสำหรับการเปรียบเทียบความต่างก่อนและหลังผ่าตัดของระดับฮีโมโกลบินในเลือดและอุบัติการณ์การได้เลือดระหว่างผ่าตัด อย่างไรก็ตามพบว่าการให้ยาทรานแซมิกเอซิดเสริมระหว่างผ่าตัดลดลงในกลุ่มที่ได้รับยาทรานแซมิกเอซิดเมื่อเทียบกับกลุ่มควบคุม (ร้อยละ 4.4 เปรียบเทียบกับร้อยละ 22.2,  $p = 0.03$ ) และไม่พบรายงานผลข้างเคียงที่สัมพันธ์กับการใช้ยาทรานแซมิกเอซิดในการศึกษานี้

**สรุป:** การให้ยาทรานแซมิกเอซิดก่อนผ่าตัดไม่มีประสิทธิผลในการลดการเสียเลือดในสตรีกลุ่มเสี่ยงที่จะผ่าตัดยากที่ได้รับการผ่าตัดมดลูกแบบเปิดหน้าท้องชนิดที่ไม่ใช่มะเร็ง

**คำสำคัญ:** ยาทรานแซมิกเอซิด, การผ่าตัดมดลูกแบบเปิดหน้าท้องชนิดผ่าตัดยาก, การลดการเสียเลือดระหว่างผ่าตัด

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## Introduction

A total abdominal hysterectomy (TAH) is a common gynecologic procedure, with over 600,000 cases performed annually<sup>(1)</sup>. At Khon Kaen Hospital, benign TAH procedures are performed approximately 500 times per year, with indications such as uterine leiomyoma, adenomyosis, and adnexal tumors.

Excessive intraoperative hemorrhage represents the most prevalent complication documented across multiple studies, with reported incidence rates spanning from 2.4% to 55.3%<sup>(2)</sup>. A consistent correlation has been observed; whereby greater volumes of blood loss are associated with increased rates of complications and resource utilization. The median estimated blood loss in these studies ranges from 238 to 660.5 mL<sup>(3)</sup>.

In 2009, research on hysterectomy patients established that an estimated blood loss of over 500 mL is a critical threshold linked to a higher risk of complications and increased need for blood transfusions and reoperations<sup>(2)</sup>. To control intraoperative bleeding during a TAH, surgeons use multiple techniques. These include pharmacological agents like intramyometrial vasopressin<sup>(4)</sup>, rectal misoprostol suppository<sup>(5)</sup> and intravenous tranexamic acid<sup>(6)</sup>, as well as surgical methods such as uterine artery ligation<sup>(7)</sup>.

Tranexamic acid (TXA) is a lysine derivative that reduces bleeding by inhibiting fibrinolysis and stabilizing blood clots. To be effective, an initial concentration of 10 mg/L is necessary, and this therapeutic level is maintained for approximately 2.9 hours after the transfusion ends<sup>(8)</sup>. TXA has a half-life of approximately 2 hours, with 95% of the drug excreted renally. A 2022 meta-analysis demonstrated that the prophylactic administration of TXA significantly reduces intraoperative blood loss during benign hysterectomies<sup>(6)</sup>.

Evidence supporting the effectiveness of TXA is limited in certain patient groups, especially those undergoing 'difficult operations.' A difficult hysterectomy is defined as a procedure performed on patients with risk factors that distort pelvic anatomy or complicate

surgical access including previous abdominal surgery, previous cesarean section (CS), uterine weight over 250 grams (or a size equivalent to a 12-week pregnancy), body mass index (BMI) above 25 kg/m<sup>2</sup>, and endometriosis or tubo-ovarian abscess (TOA) history, which can contribute to increased surgical difficulty and a higher risk of complications<sup>(2, 9, 10)</sup>.

Accordingly, this research aimed to evaluate the effectiveness of TXA in reducing intraoperative loss during difficult surgical procedures as the primary objective. The secondary objectives were the rate of massive intraoperative blood loss more than 500 mL, blood transfusion and any associated adverse events, including gastrointestinal, cardiovascular, cutaneous, and neurological manifestations<sup>(11, 12)</sup>.

## Materials and Methods

The double-blind randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital, from September 2024 to July 2025. The protocol was reviewed and ethically approved by the Khon Kaen Hospital Institute Review Board for Human Research (KEF67012) and registered to the Thai Clinical Trials Registry (TCTR20250206001). All patients provided informed consent before enrollment.

This study enrolled a total of 316 women, aged 18 years or older, who were scheduled for a benign abdominal hysterectomy, with or without adnexal surgery, and presented with one or more risk factors for a difficult procedure. These risk factors were defined as a BMI  $\geq 25$  kg/m<sup>2</sup>, diagnosis of endometriosis or TOA, uterine weight over 250 g or a size equivalent to a 12-week pregnancy, determined by bimanual examination or calculated using the geometric formula for a prolate ellipsoid ( $\text{gm} = 0.5236 \times \text{Length (L)} \times \text{Width (W)} \times \text{Anteroposterior diameter (AP)}$ )<sup>(13)</sup>, and previous abdominal surgery. Exclusion criteria included (a) active cardiovascular diseases, (b) uncontrolled hypertension (blood pressure  $> 180/110$  mmHg), (c) end-stage renal disease (creatinine clearance  $< 30$  ml/min), (d) hematologic coagulopathies, (e) gynecologic malignancies confirmed pathologically, (f)

receipt of anticoagulant drugs, (g) tranexamic acid allergy, (h) previous case of a venous thromboembolism event, or (i) receipt of enoxaparin prophylaxis before surgery.

The participants were randomly assigned to the TXA or the control group using a computer-generated sequence with block of 4. Allocation concealment was performed using an opaque, sealed envelope. According to the randomization protocol, a pharmacist prepared the study drug or placebo in identical syringes containing either 1 gram (20 mL) of TXA or 20 mL of normal saline, using standard sterile techniques. To ensure an unbiased outcome, the participants, surgeons, anesthesiologists, and outcome assessors were appropriately blinded.

On the day of surgery, the assigned nurse opened the opaque envelope, then added the anonymous solution from identical syringes that contained either 1 gram (20 mL) of TXA or 20 mL of normal saline in normal saline solution up to 100 mL. The prepared solution was transferred to the operating room in a concealed plastic container to ensure that the intervention was blinded for the surgical team. Before surgery, the study group received 10 mg/kg tranexamic acid (maximum 1 g) in normal saline, administered intravenously at 100 mL over 15 minutes before skin incision. The control group received 0.2 mL/kg of normal saline diluted with normal saline to 100 mL via an intravenous infusion 15 minutes before incision with slow infusion by an anesthesiologist. All surgical procedures (TAH, with or without adnexal surgery) were performed by randomly attending staff using standard surgical techniques. Additional TXA was administered intraoperatively when the surgeon assessed that excessive bleeding had occurred or hemostasis was difficult to achieve despite standard surgical techniques. The recommended dosage was 10 mg/kg (maximum 1 g), administered 30 minutes after the initial dose<sup>(14, 15)</sup>.

The primary outcome, intraoperative blood loss, was measured by trained and standardized operative nurses using the gravimetric method. This technique calculates total blood loss by determining the difference

between the weight of a blood-soaked and dry surgical sheet, with the volume of blood collected in a suction bottle, based on a conversion rate of 1 gram per 1 mL<sup>(13, 16, 17)</sup>.

Secondary outcomes included pre- and post-operative hemoglobin levels (assessed 24 hours after surgery), operative time, and the incidence of blood transfusions (administered when hemoglobin levels were less than 7 g/dL).

Postoperatively, adverse effects associated with TXA during hospitalization, including symptoms such as abdominal pain, nausea, vomiting, diarrhea, and thrombotic events, were documented within 24 hours after drug administration. Participants were discharged after meeting specific criteria for a minimum of 24 hours, including stable vital signs, a body temperature of 37.8 °C or less, independent ambulation, and tolerance of a regular diet. Additionally, they had to be free of symptoms such as vaginal bleeding, signs of infection, or other complications.

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{(X_1 - X_2)^2}$$

$$\sigma^2 = \text{pool variance} = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}$$

The sample size for this study was determined from a pilot study involving 30 patients, with 15 patients allocated to each group. The calculation was conducted with power at 80% at an alpha level of 0.05 and included a 5% dropout rate. The average intraoperative blood loss in the TXA group was 271.59 mL with a standard deviation (SD) of 214.65 mL, whereas the control group demonstrated a mean blood loss of 449.06 mL with an SD of 358.7 mL. Ultimately, a total of 92 women were included in the final analysis, with 46 in each group.

Statistical analysis was conducted using an intention-to-treat approach with R (version 4.5.1). Continuous variables were analyzed using the student's t-test or Wilcoxon rank-sum test and were reported as mean (SD) or median (interquartile range, IQR) for skewed data. Categorical variables were

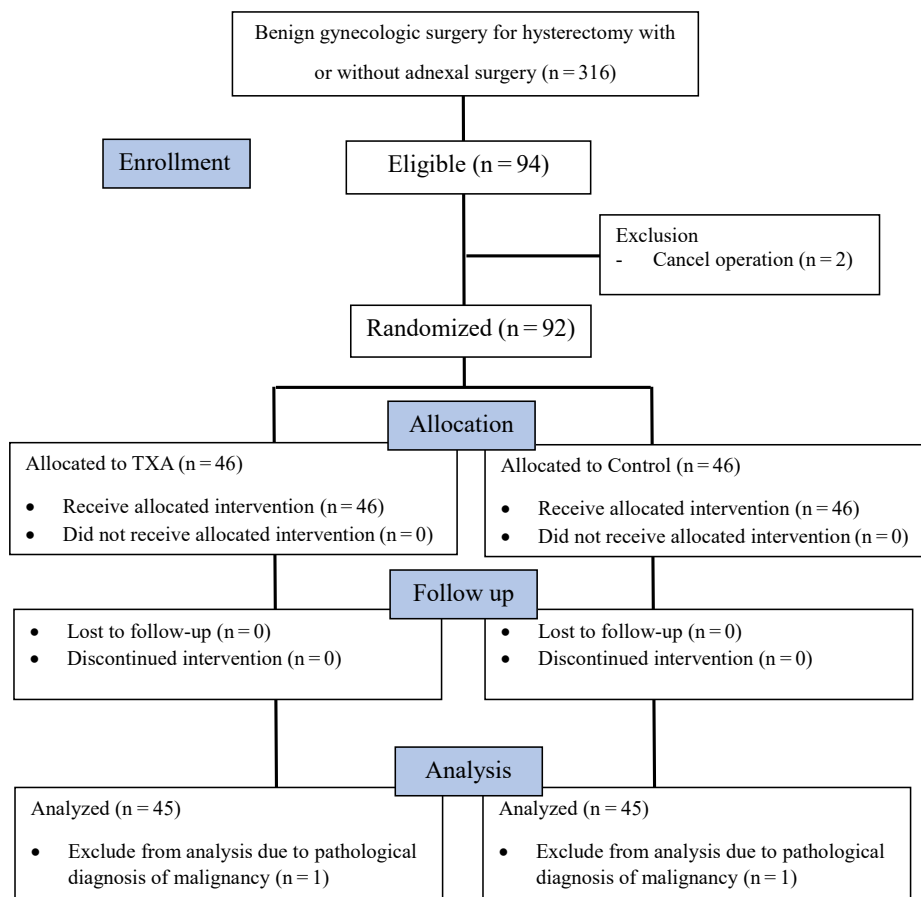
analyzed using the chi-squared test or Fisher's exact test and are reported as percentages. A p value of < 0.05 was considered statistically significant.

## Results

Between September 2024 and July 2025, 94 participants were assessed for eligibility. Two of these participants were excluded prior to randomization due to the cancellation of their operations. The remaining 92 women, who had benign gynecological conditions and risk factors for difficult hysterectomies, were then randomized. One

participant from each group was withdrawn from the study after a postoperative pathological diagnosis of malignancy. Consequently, 45 participants from the TXA group and 45 from the control group were included in the final analysis (Fig. 1).

The demographic data and clinical characteristics between the groups were similar, including age, weight, height, body mass index, underlying diseases, history of previous abdominal surgery, uterine size and weight, operation type, operative time, and surgeon experience, except for the type of skin incision (Table 1).



**Fig. 1.** Consort flow diagram.

**Table 1.** Baseline characteristics.

|                                          | TXA group<br>(n = 45) | Control group<br>(n = 45) | p value |
|------------------------------------------|-----------------------|---------------------------|---------|
| Age (years), mean $\pm$ SD               | 45.6 $\pm$ 5.1        | 47.0 $\pm$ 6.6            | 0.247   |
| Body weight (kg), mean $\pm$ SD          | 65.3 $\pm$ 10.2       | 67.7 $\pm$ 13.3           | 0.349   |
| Height (cm), median (IQR)                | 156 (153,160)         | 158 (152,160)             | 0.339   |
| BMI (kg/m <sup>2</sup> ), median (IQR)   | 27.5 (23.8, 29.4)     | 27.3 (24.0, 29.4)         | 0.942   |
| Co-morbid diseases, n (%)                |                       |                           |         |
| Diabetes mellitus                        | 2 (4.4)               | 6 (13.3)                  | 0.266   |
| Hypertension                             | 9 (20.0)              | 8 (17.8)                  | 0.788   |
| Dyslipidemia                             | 1 (2.2)               | 1 (2.2)                   | 1.000   |
| Others                                   | 6 (13.3)              | 11 (24.4)                 | 0.281   |
| Indication for surgery, n (%)            |                       |                           |         |
| Leiomyoma                                | 26 (57.7)             | 34 (75.5)                 | 0.117   |
| Leiomyoma with endometriosis             | 5 (11.1)              | 6 (13.3)                  | 1.000   |
| Adenomyosis                              | 7 (15.6)              | 3 (6.7)                   | 0.315   |
| Adenomyosis with endometriosis           | 4 (8.9)               | 0 (0.0)                   | 0.117   |
| Endometrioma                             | 3 (6.7)               | 2 (4.4)                   | 1.000   |
| Previous abdominal surgery, n (%)        | 33 (73.3)             | 30 (66.7)                 | 0.646   |
| major surgery, n (%)                     | 23 (51.1)             | 19 (42.2)                 | 0.526   |
| Operation, n (%)                         |                       |                           |         |
| TAH with BS                              | 9 (20)                | 9 (20)                    | 1.000   |
| TAH with BSO                             | 31 (68.9)             | 33 (73.3)                 | 0.642   |
| TAH with unilateral SO                   | 5 (11.1)              | 3 (6.7)                   | 0.459   |
| Uterine size by ultrasound, median (IQR) | 409 (239, 748)        | 528 (306, 816)            | 0.516   |
| Uterine weight (gm), median (IQR)        | 509 (281, 872)        | 506 (315, 852)            | 0.597   |
| Incision type, n (%)                     |                       |                           |         |
| Low midline                              | 14 (31.1)             | 25 (55.6)                 | 0.03    |
| Pfannenstiel                             | 31 (68.9)             | 20 (44.4)                 |         |
| Surgeon Experience, n (%)                |                       |                           |         |
| > 5 years                                | 33 (73.3)             | 31 (68.9)                 | 0.816   |

TXA: tranexamic acid, IQR: interquartile range, cm: centimeter, kg/m<sup>2</sup>: kilograms per meters squared, SD: standard deviation, dL: deciliter, gm: gram; TAH: total abdominal hysterectomy, BS: bilateral salpingectomy, SO: salpingo-oophorectomy, BSO: bilateral salpingo-oophorectomy

The primary outcome, the measurement of intraoperative blood loss, did not differ between the TXA group and the control group (median [IQR]: 239 [104, 384] mL vs 280 [187, 400] mL,  $p = 0.24$ ) (Table 2). Regarding the secondary outcomes, the mean difference in pre- and postoperative hemoglobin levels between the TXA and control groups was 0.3 g/dL,  $p = 0.59$  ( $0.9 \pm 1.5$  vs  $1.2 \pm 1.5$  g/dL). Moreover, the mean difference in hematocrit between the TXA and control groups was 0.5%,  $p = 0.61$  ( $3.1 \pm 4.9$  vs  $3.6 \pm 4.9\%$ ).

These data are presented in Table 2.

There was no significant difference in the incidence of intraoperative blood loss  $\geq 500$  mL (11.1% vs 22.2%,  $p = 0.26$ ), and no difference in blood transfusion rates (8 vs 6 patients,  $p = 0.84$ ). However, the TXA group demonstrated a significant reduction in the need for additional perioperative tranexamic acid injections (4.4% vs 22.2%,  $p = 0.03$ ). No thromboembolic or adverse events were reported. These findings are presented in Table 2.

**Table 2.** Primary and secondary outcomes.

|                                                | TXA group<br>(n = 45) | Control group<br>(n = 45) | 95%CI           | p value |
|------------------------------------------------|-----------------------|---------------------------|-----------------|---------|
| Measurement of blood loss (mL), median (IQR)   | 239<br>(104, 384)     | 280<br>(187, 400)         | (-207.9, 40.4)  | 0.242   |
| Measurement of blood loss $\geq 500$ mL, n (%) | 5 (11.1)              | 10 (22.2)                 | (0.63, 9.29)    | 0.258   |
| Hemoglobin level (g/dL), mean $\pm$ SD         | $0.9 \pm 1.5$         | $1.2 \pm 1.5$             | (-0.93, 0.33)   | 0.355   |
| Hematocrit (%), mean $\pm$ SD                  | $3.1 \pm 4.9$         | $3.6 \pm 4.9$             | (-2.62, 1.53)   | 0.607   |
| Operative time (min), mean $\pm$ SD            | $110.8 \pm 34.9$      | $110.7 \pm 29.4$          | (-13.40, 13.60) | 0.984   |
| Additional tranexamic acid, n (%)              | 2 (4.4)               | 10 (22.2)                 | (1.17, 60.21)   | 0.026   |
| Blood transfusion, n (%)                       | 8 (17.8)              | 6 (14.0)                  | (0.19, 2.75)    | 0.842   |

TXA: tranexamic acid, mL: milliliter, dL: deciliter, IQR: interquartile range, SD: standard deviation, g/dL: grams per deciliter, min: minutes, MD: mean difference

## Discussion

Preoperative TXA did not reduce intraoperative blood loss (239 mL vs 280 mL). However, the TXA group showed a significant reduction in the need for additional perioperative TXA, supporting its role as a beneficial adjunct in perioperative blood management. The absence of thromboembolic and other serious adverse events affirmed the safety of the drug.

These results aligned with the findings of Bahadori et al<sup>(18)</sup>, whose study investigated the effects of 1 g of prophylactic tranexamic acid in 80 women undergoing abdominal or vaginal hysterectomies for benign or malignant indications and reported no significant differences in hemoglobin levels between the two groups, before and after surgery ( $12 \pm 1.5$  vs

$12.1 \pm 1.6$  g/dL,  $p = 0.91$ ). However, the tranexamic acid group had significantly lower transfusion requirements and a shorter recovery stay. This study also revealed that preoperative TXA did not reduce intraoperative blood loss.

Topsoee et al<sup>(19)</sup> administered 1 g of prophylactic TXA to 332 women undergoing hysterectomy. Their study demonstrated a significant reduction in blood loss, both subjectively (98.4 mL vs 134.8 mL,  $p = 0.006$ ) and objectively (100.0 mL vs 166.0 mL,  $p = 0.004$ ). The rate of blood loss of 500 mL or more was also lower in the tranexamic acid group (6 vs 21 cases,  $p = 0.003$ ). However, they investigated overall benign hysterectomies with all routes of hysterectomy, not specifically complex cases such as those examined in our study. Nonetheless, the current

study's findings (11.1% vs 22.2%) were consistent with their results.

Additionally, in this study, the findings on prophylactic TXA showed a non-significant trend toward reduced blood loss, in contrast to the significant reduction reported by Nandi et al<sup>(20)</sup>, which involved 108 women undergoing abdominal or vaginal hysterectomies, who received 1 gram of intravenous tranexamic acid preoperatively. The results showed a significant reduction in blood loss, with a decrease of 259 mL compared to 185.6 mL in their control group, ranging from 141.8 to 229.5 mL ( $p < 0.001$ ). This discrepancy is likely due to differences in the patient populations. The current study focused on difficult hysterectomy cases, often characterized by a BMI  $\geq 25$  kg/m<sup>2</sup>, whereas Nandi et al included patients with smaller uterine sizes (14 weeks or less). These variations in patient characteristics, which directly affect surgical complexity and intraoperative blood loss, likely explain the varying outcomes.

Similarly, Arthi et al<sup>(21)</sup> conducted a randomized controlled trial comparing 15mg/kg of tranexamic acid intravenous 15 minutes before incision with a placebo in 100 women undergoing elective abdominal hysterectomy. They reported that the mean blood loss was significantly lower in the TXA group (mean 360 mL) compared to the placebo group (540 mL) ( $p = 0.0001$ ).

The previous study aligned with the study by Sirithunyalak et al, which conducted a double-blind randomized controlled trial evaluating a single 15 mg/kg intravenous dose of TXA in women who were diagnosed with endometrial cancer and undergoing surgical staging, demonstrated that intraoperative blood loss was significantly lower in the TXA group compared to the placebo group (295.88 mL vs 613.94 mL,  $p < 0.001$ )<sup>(22)</sup>. The doses of TXA used in their study were higher than those used in our study and included additional procedures, which might have affected the outcomes.

In contrast, our study suggested that variations in TXA dosage may influence its efficacy in reducing blood loss. Yang et al studied cytoreductive surgery

in ovarian cancer patients to compare high-dose TXA (20 mg/kg of TXA followed by 5 mg/kg/hr continuous infusion) with low-dose TXA (10 mg/kg of TXA followed by 1 mg/kg/h). The results indicated that higher doses of TXA were more effective in mitigating intraoperative bleeding and the subsequent need for blood transfusions<sup>(23)</sup>. Our results found that a lower dose (10 mg/kg) only showed a trend toward reduction without statistical significance for the primary outcome ( $p = 0.24$ ).

Furthermore, Sirithunyalak et al highlighted that in malignancy surgeries, there was a significant correlation with massive intraoperative blood loss, making the hemostatic effect of TXA more easily detectable<sup>(22)</sup>. The present study demonstrated a significant difference in the need for additional perioperative TXA in the intervention group (4.4% vs 22.2%,  $p = 0.03$ ). This suggests that preoperative TXA stabilizes early clot formation and improves the surgical field, thereby reducing clinicians' reliance on adjunct hemostatic measures. However, our study focused on difficult operations characterized by dense adhesions and large uterine size, which often result in persistent capillary oozing and ongoing microvascular bleeding. Nonetheless, these factors may not always lead to significant volumetric differences.

Furthermore, Wongjariyakul et al demonstrated that 1 gram of preoperative TXA in women at high risk for postpartum hemorrhage who were scheduled for cesarean section was effective in reducing intraoperative blood loss compared to a placebo<sup>(24)</sup>.

In addition, using meta-analyses, Ahmed Abu-Zaid et al<sup>(6)</sup> demonstrated that preoperative tranexamic acid was safe and showed a trend toward reducing estimated intraoperative blood loss. This current study focused specifically on difficult abdominal hysterectomy cases involving factors such as prior abdominal surgery, large uterine size, high BMI, and pelvic adhesions. These conditions might increase blood loss and necessitate additional perioperative TXA. The variability among participants in the two studies might explain the different outcomes.

In the current study, the Pfannenstiel incision was observed at a higher rate in the TXA group. The median [IQR] uterine weight was 509 [281, 872] g in the TXA group and 506 [315, 852] g in the control group. These values reflect the complexity of the procedure, which often involves large uterine sizes, a characteristic of difficult hysterectomies. In particular, a uterine weight of over 500 g is associated with intraoperative blood loss exceeding 500 ml. Thus, a larger uterine size and a different incision might restrict the ability to identify a statistically significant reduction in blood loss, despite observing a clinical benefit.

Finally, Phupong provided a comprehensive review of the role of TXA in obstetrics and gynecology, noting its established efficacy in treating postpartum hemorrhage and heavy menstrual bleeding. Nevertheless, the evidence supporting its benefit in broad gynecological surgeries remains limited, and further studies are thus necessary in order to solidify its routine use in this field<sup>(25)</sup>.

The strengths of the current study included its randomized, double-blind, placebo-controlled design, low dropout rate, and the measurement of intraoperative blood loss using a validated and precise formula. Additionally, the trial demonstrated a significant reduction in the additional perioperative tranexamic acid injections, suggesting that tranexamic acid provides a meaningful hemostatic benefit, even in high-risk hysterectomy cases. A limitation of this study was that it did not determine whether differences between the surgeons (general gynecologists and oncologic gynecologists) might affect surgical techniques. Therefore, it is recommended that further studies should be conducted in order to explore various approaches to hysterectomy.

## Conclusion

Prophylactic intravenous TXA did not reduce intraoperative blood loss or transfusion requirements in difficult abdominal hysterectomy for benign gynecological disease. However, it significantly reduced the use of additional perioperative TXA, and

no serious adverse events were observed.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## OBSTETRICS

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# Preeclampsia and Pregnancy outcome in Pregnant Women with Gestational Hypertension at Chonburi Hospital

Achiraya Wangsri, M.D.\*,  
Siriporn Trainak M.D.\*

*\* Department of Obstetrics and Gynecology, Chonburi Hospital, Chonburi, Thailand*

### ABSTRACT

**Objectives:** To determine the incidence of preeclampsia (PE) and pregnancy outcome in women diagnosed with gestational hypertension (GH) at Chonburi Hospital.

**Materials and Methods:** This combined retrospective-prospective cohort study collected the data of pregnant women diagnosed GH between January 2019 and April 2025. Pregnant women with chronic hypertension, abortion, or multifetal gestation were excluded. The data predicting progression from GH to PE were analyzed by logistic regression analysis.

**Results:** 238 pregnancies with GH were enrolled and followed until delivery. 12 of these (5.0%) lost to follow-up or delivery at other hospitals. 58 pregnant women (25.7%, 95% confidence interval (CI) 20.10, 31.88%) developed preeclampsia, and 38 of these cases (16.8%, 95% CI 8.39, 17.41%) were classified as having severe features. Logistic regression reveals that the patient diagnosed with GH before 34 weeks had a higher risk of developing PE (adjusted odds ratio (OR) 3.30, 95% CI 1.65, 6.61). Additionally, women with diastolic blood pressure  $\geq 100$  mmHg at diagnosis also had a higher risk of PE progression (adjusted OR 3.16, 95% CI 1.58, 6.34). The pregnant women with PE progression had higher rate of cesarean section (relative risk (RR) 1.69, 95% CI 1.44, 1.98), early preterm birth (RR 8.69, 95% CI 1.80, 41.86), late preterm birth (RR 5.07, 95% CI 2.66, 9.65) and low birth weight (RR 4.34, 95% CI 2.37, 7.97).

**Conclusion:** PE progression occurred for a quarter number in GH pregnant women. The risks of PE progression are early gestational age of GH diagnosis and high diastolic blood pressure at diagnosis. Adverse pregnancy outcomes in preeclampsia women are preterm delivery and high cesarean section rate.

**Keywords:** gestational hypertension, preeclampsia, pregnancy induced hypertension, hypertensive disorder of pregnancy, diastolic blood pressure, preterm delivery, cesarean section.

**Correspondence to:** Achiraya Wangsri, M.D., Department of Obstetrics and Gynecology, Chonburi Hospital, Chonburi, Thailand. E-mail: jijichichi@gmail.com

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# อุบัติการณ์การเกิดภาวะครรภ์เป็นพิษในหญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงขณะตั้งครรภ์ในโรงพยาบาลชลบุรี

อชิรญา วงศ์ศรี, สิริพร ไตรนาค

## บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาอุบัติการณ์การเกิดภาวะครรภ์เป็นพิษและครรภ์เป็นพิษรุนแรงในหญิงตั้งครรภ์ที่มีภาวะความดันสูงขณะตั้งครรภ์ในโรงพยาบาลชลบุรี

**วัสดุและวิธีการ:** เป็นการศึกษาเชิงพรรณนาแบบย้อนหลังโดยศึกษาจากเวชระเบียนของโรงพยาบาลชลบุรี ร่วมกับการศึกษาเชิงพรรณนาแบบไปข้างหน้า รวบรวมผู้ป่วยที่วินิจฉัยภาวะความดันโลหิตสูงขณะตั้งครรภ์ในช่วงเดือนมกราคม พ.ศ. 2562 - เดือนเมษายน พ.ศ. 2568 โดยตัดกลุ่มผู้ป่วยที่เคยได้รับการวินิจฉัยว่าเป็นความดันโลหิตสูง ผู้ที่มีภาวะแท้ง หรือมีภาวะครรภ์แฝดออกจากการศึกษา ข้อมูลในเรื่องของปัจจัยต่างๆที่อาจส่งผลต่อการเกิดภาวะครรภ์เป็นพิษในหญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงถูกวิเคราะห์เพิ่มเติมโดยใช้การวิเคราะห์การถดถอยโลจิสติก

**ผลการศึกษา:** จากจำนวนหญิงตั้งครรภ์ที่ได้รับการวินิจฉัยเรื่องของภาวะความดันโลหิตสูงขณะตั้งครรภ์ทั้งหมด 226 ราย พบว่ามีการเกิดภาวะครรภ์เป็นพิษ 58 ราย (ร้อยละ 25.7, 95% CI 20.10, 31.88) โดย 38 เคสจากกลุ่มผู้ป่วยข้างต้นเกิดภาวะครรภ์เป็นพิษแบบรุนแรง (ร้อยละ 16.8, 95% CI 8.39, 17.41) จากการวิเคราะห์การถดถอยโลจิสติกพบว่าปัจจัยที่เกี่ยวข้องกับการเกิดภาวะครรภ์เป็นพิษอย่างมีนัยสำคัญมีด้วยกัน 2 ตัวแปรคืออายุครรภ์ที่วินิจฉัยภาวะความดันสูงขณะตั้งครรภ์และค่าความดันโลหิตตัวล่างในวันที่วินิจฉัย ซึ่งพบว่าในผู้ป่วยที่วินิจฉัยภาวะความดันโลหิตสูงขณะตั้งครรภ์ก่อนอายุครรภ์ 34 สัปดาห์จะเพิ่มความเสี่ยงในการเกิดภาวะครรภ์เป็นพิษ (adjusted odds ratio (OR) 2.79, 95% CI 1.40, 5.54) และในกลุ่มผู้ป่วยที่มีค่าความดันโลหิตตัวล่างตอนวินิจฉัย  $\geq 100$  มิลลิเมตรปรอทจะเพิ่มความเสี่ยงต่อการเกิดภาวะครรภ์เป็นพิษเช่นกัน (adjusted OR 2.91, 95% CI 1.24, 6.82) โดยผู้ป่วยกลุ่มที่พัฒนาไปสู่ภาวะเป็นครรภ์เป็นพิษจะพบว่าจะมีอัตราการผ่าคลอดที่สูงกว่า (relative risk (RR) 1.69, 95% CI 1.44, 1.98), อัตราคลอดก่อนกำหนดก่อน 34 สัปดาห์สูงกว่า (RR 8.69, 95% CI 1.80, 41.86), อัตราคลอดก่อนกำหนดตั้งแต่ 34 สัปดาห์เป็นต้นไปสูงกว่า (RR 5.07, 95% CI 2.66, 9.65) และอัตราคลอดบุตรน้ำหนักตัวน้อยสูงกว่ากลุ่มที่ไม่ได้พัฒนาสู่ภาวะครรภ์เป็นพิษ (RR 4.34, 95% CI 2.37, 7.97) **สรุป:** หญิงตั้งครรภ์ที่มีภาวะความดันโลหิตสูงระหว่างตั้งครรภ์พบว่ามีกว่า 1 ใน 4 ที่พัฒนาไปสู่ภาวะครรภ์เป็นพิษ ซึ่งจากงานวิจัยนี้พบว่าปัจจัยที่เกี่ยวข้องนั้นจะเป็นเรื่องของการวินิจฉัยภาวะความดันโลหิตสูงขณะตั้งครรภ์ตั้งแต่อายุครรภ์น้อยกว่า 34 สัปดาห์ และความดันโลหิตตัวล่างตอนวินิจฉัย  $\geq 100$  มิลลิเมตรปรอท

**คำสำคัญ:** ภาวะความดันโลหิตสูงขณะตั้งครรภ์, ภาวะครรภ์เป็นพิษ, ภาวะความดันโลหิตสูงที่เกิดจากการตั้งครรภ์, กลุ่มโรคความดันโลหิตสูงในระหว่างตั้งครรภ์, ความดันโลหิตตัวล่าง, การคลอดก่อนกำหนด, การผ่าตัดคลอด

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## Introduction

Hypertensive disorders of pregnancy (HDP) are a significant global health concern, with an incidence of up to 10%<sup>(1)</sup> and rising continuously. Global statistics show that the incidence of HDP increased from 16.3 million cases per year in 1990 to 18.1 million cases per year in 2010. That's rising up to 10.9% over two decades<sup>(2)</sup>. A study by Urquia found that the incidence of HDP varies across different ethnicities, weight, and behavioral factors<sup>(3)</sup>. In Thailand, the incidence of HDP is reported as 27.5 per 1,000 pregnant women<sup>(4)</sup>. Data from the Thai Ministry of Public Health in 2018 reported that there were 15 maternal deaths per 100,000 live births during pregnancy, labor, and postpartum that were caused by HDP, accounting for 29% of direct maternal deaths<sup>(5)</sup>.

The exact cause of HDP is still unknown, but several hypotheses have been proposed, including chronic placental ischemia, genetic predisposition, and the maternal immune response to placental cells in the bloodstream. It is likely a multifactorial condition<sup>(6)</sup>. According to the American College of Obstetricians and Gynecologists (ACOG) 2020 classification, HDP is divided into four main categories<sup>(6)</sup> including gestational hypertension, chronic hypertension, preeclampsia-eclampsia, and chronic hypertension with superimposed preeclampsia. Globally, the incidence of these conditions in pregnant women is 2-17%, 3-5%, 5-8%, and 0.75-1.25%, respectively<sup>(1, 7)</sup>.

Gestational hypertension (GH) is generally considered the mildest form of HDP. Typically, it does not require treatment, but close monitoring of maternal blood pressure and clinical symptoms are required. Blood pressure usually returns to normal within six weeks after delivery. If blood pressure does not reach the severe range ( $\geq 160/110$  mmHg), fetal outcomes are not significantly different from normal pregnancy<sup>(8)</sup>. However, women with GH are at a 3-5 times higher risk of developing preeclampsia or eclampsia compared to the general pregnant population<sup>(1, 9)</sup>. This progression can lead to severe maternal and fetal morbidity and mortality. Therefore, early identifying

and preventing risk factors of the progression from GH to preeclampsia could improve pregnancy outcomes.

Several research studies have focused on this progression. In Northern Ethiopia, the GH incidence was 6%. Among women with GH, 17.1% developed preeclampsia<sup>(9)</sup>. Similarly, the study from Australia showed that 15-25% progression rate from GH to preeclampsia<sup>(10)</sup>. While a prospective cohort study in Taiwan showed that the GH incidence was 5.4%. Up to 42.1% of GH developed preeclampsia<sup>(11)</sup>. This is consistent with a study from the U.S. which found that 46% of GH pregnancies progressed to preeclampsia, with 9.6% of these cases being severe<sup>(12)</sup>.

The previous studies revealed several predictive risk factors associated with the progression of GH to preeclampsia such as maternal age, body mass index (BMI), parity, history of miscarriage, excessive maternal weight gain during pregnancy, and grade III preterm placental calcification (PPC) from ultrasound<sup>(9-12)</sup>.

Due to the diversity of previous evidence about the progression rate from GH to preeclampsia and there is lacking data in Thai population. Our study focused on the incidence of progression from GH to preeclampsia in Chonburi Hospital. The data of suspected factors associated with preeclampsia progression such as baseline characteristics at the time of presentation and pregnancy outcomes also had been collected and analyzed.

## Materials and Methods

This combined retrospective and prospective cohort study was conducted at Chonburi Hospital, Tertiary public hospital of Eastern Thailand. This study included women diagnosed GH in antenatal care clinic between January 2019 and April 2025. The sample size was calculated using Cochran's formula with the incidence of 17% from previous literature review, a margin of error of 0.05, and a 95% confidence level. The required sample size was 217 participants. To mitigate the risk of subject attrition, the initial sample size of 217 was inflated by 10%, establishing a final

requirement of 239 participants. The study was approved by the local Institutional Review Board of the hospital.

GH was defined as the new onset of hypertension (systolic blood pressure (SBP)  $\geq 140$  mmHg and/or diastolic blood pressure (DBP)  $\geq 90$  mmHg) after 20 weeks of gestation without the presence of proteinuria or end-organ damage. Preeclampsia without severe features was defined as the new onset of hypertension after 20 weeks of gestation with the presence of proteinuria. In this study, a urinary protein-to-creatinine ratio (UPCR) of  $\geq 0.3$  was used to assess for proteinuria. New onset of hypertension detected after 20 weeks of gestation was classified as preeclampsia with severe features if any clinical sign of end-organ damage was present, including; SBP  $\geq 160$  mmHg, DBP  $\geq 110$  mmHg, Thrombocytopenia (platelet count  $< 100,000$  cell/mm<sup>3</sup>), renal insufficiency (creatinine  $\geq 1.1$  mg/dL or a doubling of serum creatinine baseline), impair liver function (an aspartate aminotransferase / alanine aminotransferase rising  $\geq 2$ x of normal concentration), pulmonary edema, and new-onset persistent headache or visual disturbances<sup>(6)</sup>.

Exclusion criteria included a history of essential hypertension or secondary hypertension due to their known underlying diseases (e.g. hyperthyroid, pheochromocytoma, known case chronic kidney disease; creatinine  $> 1.1$  mg/dl), multiple gestation, and termination of pregnancy before 24 weeks. Moreover, patients who did not deliver at Chonburi Hospital or had incomplete data about the onset of hypertension and laboratory test were excluded.

Clinical and laboratory data were recorded at the time of presentation. These data included patient age, body weight (both prepregnancy and at delivery), BMI, blood pressure at diagnosis, history of HDP, and history of abortion. The patient's diabetes mellitus (DM) status, including overt DM and gestational diabetes mellitus (GDM), and aspirin prescription during this pregnancy were also documented. Laboratory data consisting of complete blood count, creatinine, aspartate aminotransferase, alanine

aminotransferase, UPCR, and international normalized ratio, were also collected. Excessive weight gain was defined according to prepregnancy BMI<sup>(1)</sup>.

In our study, patients who were at moderate to high risk of preeclampsia, according to the American College of Obstetricians and Gynecologists Committee Opinion on low-dose aspirin use during pregnancy<sup>(13)</sup>, were prescribed aspirin.

Blood pressure monitoring in our study was standardized by using the same model of digital sphygmomanometer, calibrated annually by iTRIS Medical Co., Ltd. If a patient's blood pressure is found to be in the hypertensive range, the patient will be advised to rest and wait for a repeated measurement in four hours, according to criteria diagnosis of hypertension.

All pregnant women with GH were followed-up at Chonburi Hospital every 1 to 2 weeks until delivery. At every visit, blood pressure was measured as described and urine protein screening was performed using a dipstick. If the blood pressure measurement at any visit shown in hypertensive range, the patient underwent laboratory blood testing and UPCR testing. All participants were advised regarding the signs of preeclampsia with severe features and were instructed to perform home blood pressure monitoring and record the results.

The patients were followed-up until delivery. Pregnancy outcomes such as route of delivery, gestational age at delivery, Neonatal birth weight, APGAR score, serious pregnancy outcomes were collected.

Data were collected and analyzed using STATA/MP version 16.0. Participant characteristics and outcomes were compared using a Pearson chi-squared test for categorical variables and two-tailed student's t-test for continuous variables. A  $p < 0.05$  was considered significant. Multiple logistic regression analysis was performed to assess the effects of the significant variables as predictors of preeclampsia progression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjusting for potential confounding factors discovered in this study.

## Results

The study period was January 2019 to April 2025. A total of 238 pregnant women with GH were enrolled. Initial data were obtained from a retrospective cohort study of 198 participants. The sample size was enhanced by the extension of data collection through a prospective cohort study, yielding an additional 40 participants. All of them were followed-up until delivery. 12 of these (5.0%) were lost to follow-up and delivery at other hospitals. The remaining 226 participants were collected the data for analysis. 58 cases progressed to preeclampsia (25.7%, 95% CI 20.10, 31.88%), with 38 cases (16.8%, 95% CI 8.39, 17.41%) developing severe features. The mean of gestational

age at which patients progressed to preeclampsia was  $36.05 \pm 2.13$  weeks.

The baseline characteristics of the women with GH alone (GH-GH group) and GH who progressed to preeclampsia (GH-PE group) are presented in Table 1. There were significant differences in gestational age at diagnosis and DBP at first time diagnosis between these two groups. The GH-PE group had a significantly earlier diagnosis of GH ( $33.63 \pm 3.18$  weeks) compared to the GH-GH group ( $35.46 \pm 4.21$  weeks,  $p = 0.003$ ). Additionally, the mean DBP at the time of initial diagnosis of GH was significantly higher in the GH-PE group ( $99.14 \pm 5.78$  mmHg) compared to the GH-GH group ( $96.14 \pm 4.32$  mmHg,  $p < 0.001$ ).

**Table 1.** Baseline characteristic at the presentation between GH-GH group and GH-PE group.

| Variables                                                  | GH-GH (n = 168)   | GH-PE (n = 58)    | p value |
|------------------------------------------------------------|-------------------|-------------------|---------|
| Maternal age (years), mean $\pm$ SD                        | $30.75 \pm 7.02$  | $31.64 \pm 6.28$  | 0.395   |
| Prepregnancy BMI ( $\text{kg}/\text{m}^2$ ), mean $\pm$ SD | $29.92 \pm 6.47$  | $28.21 \pm 4.73$  | 0.066   |
| < 25 $\text{kg}/\text{m}^2$ , n (%)                        | 39 (23.2%)        | 16 (27.6%)        | 0.504   |
| 25-30 $\text{kg}/\text{m}^2$ , n (%)                       | 54 (32.1%)        | 21 (36.2%)        | 0.571   |
| $\geq 30$ $\text{kg}/\text{m}^2$ , n (%)                   | 75 (44.6%)        | 21 (36.2%)        | 0.262   |
| Nulliparous, n (%)                                         | 60 (35.7%)        | 23 (39.6%)        | 0.591   |
| History of abortion, n (%)                                 | 29 (17.3%)        | 9 (15.5%)         | 0.759   |
| History of HDP, n (%)                                      | 5 (3.0%)          | 3 (5.2%)          | 0.435   |
| Diabetes mellitus status                                   |                   |                   |         |
| GDM (diet control), n (%)                                  | 20 (11.9%)        | 10 (17.2%)        | 0.302   |
| GDM (medication control), n (%)                            | 18 (10.7%)        | 5 (8.6%)          | 0.649   |
| Known case DM, n (%)                                       | 4 (2.4%)          | 4 (6.9%)          | 0.109   |
| Aspirin prescription, n (%)                                | 23 (13.7%)        | 8 (13.8%)         | 0.984   |
| Gestational age at 1st diagnosis GH (weeks), mean $\pm$ SD | $35.46 \pm 4.21$  | $33.63 \pm 3.18$  | 0.003   |
| SBP at 1 <sup>st</sup> diagnosis (mmHg), mean $\pm$ SD     | $149.34 \pm 5.78$ | $150.38 \pm 6.13$ | 0.246   |
| DBP at 1 <sup>st</sup> diagnosis (mmHg), mean $\pm$ SD     | $96.14 \pm 4.32$  | $99.14 \pm 5.78$  | < 0.001 |
| Excessive weight gain, n (%)                               | 116 (69.0%)       | 41 (70.7%)        | 0.8153  |
| Hemoglobin at diagnosis (g/dL), mean $\pm$ SD              | $12.19 \pm 1.10$  | $12.34 \pm 1.07$  | 0.365   |

SD: standard deviation, BMI: body mass index, HDP: hypertensive disorders of pregnancy, GDM: gestational diabetes mellitus, DM: diabetes mellitus, GH: Gestational hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure.

\* Excessive weight gain was defined according to prepregnancy BMI and weight gain in second and third trimester<sup>(1)</sup>: - Prepregnancy BMI < 25  $\text{kg}/\text{m}^2$ : > 0.45  $\text{kg}/\text{week}$ , Prepregnancy BMI 25-24.99  $\text{kg}/\text{m}^2$ : 0.27  $\text{kg}/\text{week}$ , Prepregnancy BMI  $\geq 30$   $\text{kg}/\text{m}^2$ : 0.23  $\text{kg}/\text{week}$

There were no significant differences between two groups in terms of maternal age, prepregnancy BMI, nulliparity, history of HDP in previous pregnancy, history of abortion, DM status, aspirin prescription, SBP at first diagnosis, excessive weight gain, or

hemoglobin at diagnosis.

Subgroup analysis was conducted to compare women turned to preeclampsia without severe feature (GH-MPE group, n = 20) and women turned to preeclampsia with severe feature (GH-SPE group, n

= 38). The results are shown in Table 2. The gestational age at the time of GH diagnosis was not significantly different in GH-MPE group ( $34.99 \pm 2.64$ ) when compared with GH-GH group ( $35.46 \pm 4.21$ ,  $p = 0.627$ ). However, a significant difference was found in GH-SPE group ( $32.92 \pm 3.24$ ) compared with GH-GH group ( $p = 0.001$ ). Furthermore, the DBP at the time

of diagnosis was significantly higher in the GH-SPE group ( $99.87 \pm 5.84$  mmHg) compared to the GH-GH group ( $96.14 \pm 4.32$  mmHg,  $p < 0.001$ ). Conversely, there was no significant difference between GH-GH and GH-MPE group ( $96.14 \pm 4.32$ ,  $p = 0.128$ ). Other variables from Table 1 were also analyzed, but no significant difference was detected.

**Table 2.** Subgroup analysis of baseline characteristics at the presentation between GH-GH group and GH-PE group.

| Variables                               | GH-GH (n = 168)  | GH-MPE (n = 20)  | p value* | GH-SPE (n = 38)  | p value* |
|-----------------------------------------|------------------|------------------|----------|------------------|----------|
| Gestational age at diagnosis GH (weeks) | $35.46 \pm 4.21$ | $34.99 \pm 2.64$ | 0.627    | $32.92 \pm 3.24$ | 0.001    |
| DBP at 1st diagnosis (mmHg)             | $96.14 \pm 4.32$ | $97.75 \pm 5.52$ | 0.128    | $99.87 \pm 5.84$ | < 0.001  |
| Prepregnancy BMI                        |                  |                  |          |                  |          |
| < 25 kg/m <sup>2</sup> , n (%)          | 39 (23.2%)       | 6 (30%)          | 0.501    | 10 (26.3%)       | 0.677    |
| 25-30 kg/m <sup>2</sup> , n (%)         | 54 (32.1%)       | 4 (20%)          | 0.266    | 17 (44.7%)       | 0.140    |
| ≥ 30 kg/m <sup>2</sup> , n (%)          | 75 (44.6%)       | 10 (50%)         | 0.649    | 11 (28.9%)       | 0.076    |

MPE: mild preeclampsia, SPE: superimposed preeclampsia, GH: gestational hypertension, DBP: diastolic blood pressure, BMI: body mass index

\* p value compared with GH-GH group

The comparison of delivery outcomes between women GH-GH group and GH-PE group are shown in Table 3. Women with preeclampsia had a markedly higher rate of cesarean section compared with those with gestational hypertension (91.4% vs 54.2%,

relative risk (RR) 1.69, 95% CI 1.44, 1.98). After exclusion of the other obstetric causes of cesarean section such as abnormal fetal lie, previous cesarean section, the data still in the same direction (81.0% vs 42.9%, RR 1.89, 95%CI 1.52, 2.34)

**Table 3.** Comparison of pregnancy outcome between GH-GH group and GH-PE group.

| Outcomes                    | GH-GH (n = 168) | GH-PE (n = 58) | RR   | 95% CI      |
|-----------------------------|-----------------|----------------|------|-------------|
| Route of delivery           |                 |                |      |             |
| Normal labor, n (%)         | 74 (44.0%)      | 5 (8.6%)       | 0.19 | 0.08, 0.46  |
| Cesarean section, n (%)     | 91 (54.2%)      | 53 (91.4%)     | 1.69 | 1.44, 1.98  |
| Others (V/E, B/A), n (%)    | 3 (1.8%)        | 0 (0%)         | -    |             |
| Gestational age at delivery |                 |                |      |             |
| Early preterm, n (%)        | 2 (1.2%)        | 6 (10.3%)      | 8.69 | 1.80, 41.86 |
| Late preterm, n (%)         | 12 (7.1%)       | 21 (36.2%)     | 5.07 | 2.66, 9.65  |
| Birth weight (g)            |                 |                |      |             |
| 1,501-2,500 g, n (%)        | 14 (8.3%)       | 21 (36.2%)     | 4.34 | 2.37, 7.97  |
| 1,000-1,500 g, n (%)        | 1 (0.6%)        | 2 (3.4%)       | 5.79 | 0.53, 62.71 |
| < 1,000 g, n (%)            | 0 (0%)          | 0 (0%)         | -    |             |
| APGAR score at 1 min        |                 |                |      |             |
| > 7                         | 166 (98.8%)     | 54 (93.1%)     | 0.94 | 0.88, 1.01  |
| ≤ 7                         | 2 (1.2%)        | 2 (3.4%)       | 2.90 | 0.42, 20.10 |
| < 4                         | 0 (0%)          | 2 (3.4%)       | -    |             |
| Admit NICU                  | 1 (0.6%)        | 3 (5.2%)       | 8.69 | 0.92, 81.90 |

GH: gestational hypertension, PE: preeclampsia, RR: relative risk, CI: confidence interval, V/E: variant/effect, B/A: before/after, NICU: neonatal intensive care unit

The mean gestational age at delivery was significantly lower in the GH-PE group than in the GH-GH group ( $36.20 \pm 1.85$  vs  $38.04 \pm 1.52$  weeks,  $p < 0.001$ ). As a result, preeclampsia had a significant impact on preterm delivery rates, leading to an increased risk of both early preterm birth (10.3% vs 1.2%, RR 8.69, 95% CI 1.80, 41.86) and late preterm birth (36.2% vs 7.1%, RR 5.07, 95% CI 2.66, 9.65).

Significant differences were also found in neonatal outcomes. Infants born to mothers with preeclampsia had lower mean birth weights ( $2,748.17 \pm 735.68$  g vs  $3,100.23 \pm 486.03$  g,  $p < 0.001$ ). The risk of low birth weight (1,501–2,500 g) was significant higher in this group (36.2% vs 8.3%, RR 4.34, 95% CI 2.37, 7.97). However, there were no significant differences in the rates of very low birth weight (1,000–1,500 g) or extremely low birth weight ( $< 1,000$  g), Apgar scores, or neonatal intensive care unit admission between the groups. No case of abruptio placenta or postpartum intensive care unit

admission was detected in this study.

From the result above, gestational age at diagnosis and DBP at first diagnosis were significantly different in both groups. Multiple logistic regression was conducted to identify predictors for the progression to preeclampsia. We used the variables with  $p < 0.1$  from Table 1, which included gestational age at diagnosis, DBP at the first time of diagnosis, and the prepregnancy BMI, for multiple logistic regression analysis and calculation of adjusted OR.

After analysis with multiple logistic regression, we found the risk of progressing to preeclampsia was significantly higher in women diagnosed with GH before 34 weeks (adjusted OR 3.304,  $p = 0.001$ ) (Table 4). Patients with a DBP at diagnosis equal to or higher than 100 mmHg also had a significant higher risk for preeclampsia progression (adjusted OR 3.316,  $p = 0.001$ ). For the prepregnancy BMI, we found that lower prepregnancy BMI was associated with a modest increase in the risk for preeclampsia progression (adjusted OR 0.943,  $p = 0.048$ ).

**Table 4.** Results of univariate and multivariate analysis of predictors of progression to preeclampsia in gestational hypertension.

| Variables                   | Crude OR (95% CI)    | p value | Adjusted OR* (95% CI) | p value |
|-----------------------------|----------------------|---------|-----------------------|---------|
| GA at diagnosis of GH       |                      |         |                       |         |
| GA < 34 week                | 2.415 (1.279, 4.559) | 0.007   | 3.304 (1.653, 6.607)  | 0.001   |
| DBP at diagnosis            |                      |         |                       |         |
| DBP $\geq 100$ mmHg         | 2.410 (1.268, 4.580) | 0.007   | 3.159 (1.576, 6.336)  | 0.001   |
| Prepregnancy BMI            |                      |         |                       |         |
| < 25 kg/m <sup>2</sup>      | Reference            |         | Reference             |         |
| 25 - 30 kg/m <sup>2</sup>   | 0.948 (0.439, 2.047) | 0.892   | 0.990 (0.448, 2.188)  | 0.981   |
| $\geq 30$ kg/m <sup>2</sup> | 0.683 (0.320, 1.455) | 0.323   | 0.662 (0.303, 1.445)  | 0.301   |

PE: preeclampsia, GH: gestational hypertension, OR: odds ratio CI: confidence interval, GA: gestational age, DBP: diastolic blood pressure, BMI: body mass index

\* We used the variables with  $p < 0.1$  from Table 1, which included GA at diagnosis, DBP at the first time of diagnosis, and the prepregnancy BMI, for multiple logistic regression analysis and calculation of adjusted OR.

## Discussion

This study demonstrated that 25.7% of patients with GH at Chonburi Hospital developed preeclampsia. This finding was consistent with the results reported in previous research, where the rate of progression from GH to preeclampsia has been documented to range widely from 10% to 46%<sup>(9-12)</sup>. The variability in

these rates may be attributed to differences in study populations, ethnicity, and regional healthcare practices. Additionally, the data showed that an earlier diagnosis of GH, particularly before 34 weeks of gestation, was associated with a higher risk of developing preeclampsia. This supported previous findings that the timing of GH onset was important

predictors of the progression to preeclampsia, emphasizing the importance of early screening and close monitoring of pregnant women diagnosed with GH before 34 weeks<sup>(10-12)</sup>.

From previous studies, the underlying pathophysiological mechanisms of GH and preeclampsia reported that both are different. In preeclampsia, the primary causative factor involves placental abnormalities, such as abnormal placental development and pathology leading to placental ischemia. This placental insufficiency triggers a cascade of events, including endothelial dysfunction, oxidative stress, and an imbalance in angiogenic factors, which contribute to systemic hypertension and multiple organ dysfunction. In contrast, GH is thought to result predominantly from maternal factors, including altered vascular tone, increased vascular resistance, and an imbalance between cardiac output and vascular compliance, without the significant placental pathology characteristic of preeclampsia<sup>(14)</sup>.

Based on the timing of onset, preeclampsia can be classified into two main categories: early-onset preeclampsia, diagnosed before 34 weeks of gestation, and late-onset preeclampsia, diagnosed at or after 34 weeks of gestation. In this study, the mean gestational age at progression to preeclampsia was 36.05 weeks (95% CI 35.50, 36.61), which corresponded to late-onset preeclampsia. Previous studies have suggested that the development of late-onset preeclampsia may not be related to placental factors but could also involve maternal factors. Therefore, the detection of GH at an earlier stage, which reflects underlying maternal predisposition, could be a predictive factor for the subsequent development of late-onset preeclampsia<sup>(15)</sup>.

Not only was the gestational age at the diagnosis of GH identified as a key predictive factor for progression to preeclampsia in our study, but DBP at first diagnosis was also an associated factor. An increase in DBP is caused by increased systemic vascular resistance, which can serve as a reflection of maternal vascular health. From our literature review, there is no previous study directly discussed

this specific association. However, some findings were consistent with our results. Maria et al (2014)<sup>(16)</sup> reported that DBP could serve as a risk indicator for preeclampsia in normal population. They demonstrated that a baseline DBP  $\geq 80$  mmHg at 12 weeks of gestation, combined with an increase in DBP of  $\geq 15$  mmHg, could identify women at risk of preeclampsia, with a sensitivity of 92% and a specificity of 44%. But the study in GH population is still limited.

From Table 1, the baseline prepregnancy BMI was likely different between the GH-GH and GH-PE groups ( $p = 0.066$ ). However, when prepregnancy BMI was classified according to the World Health Organization classification of overweight/obesity<sup>(17)</sup>, it seemed to be no statistical difference. Multiple logistic regression analysis indicated that patients with obesity tended to have a decreased risk of preeclampsia progression, although this finding was not statistically significant. This observation was consistent with the study by Badon Sylvia et al<sup>(18)</sup>, they found that chronic hypertension women with obesity with low gestational weight gain, compared to those with normal weight and overweight, were associated with 27–54% lower risk of several adverse pregnancy outcomes, including preeclampsia and cesarean delivery. Therefore, the association between prepregnancy BMI and gestational weight gain should be further investigated.

Comparison of perinatal outcomes in this study demonstrated that the GH-PE group had a higher incidence of preterm delivery, cesarean section, and neonatal low birth weight. However, no significant differences were observed in serious neonatal outcomes, such as birth asphyxia or the need for neonatal intensive care unit admission. These findings were consistent with previous studies<sup>(11, 12)</sup> and corresponded with both the underlying pathophysiology of the disease and the current management strategies for preeclampsia.

The progression from GH to preeclampsia is associated not only with the immediate perinatal morbidity and mortality but also with an increasing

risk of long-term cardiovascular disease<sup>(19)</sup>. Therefore, identifying key risk factors for this progression is crucial for enabling early detection and prevention. These strategies could effectively reduce the long-term health complications linked to preeclampsia.

A key limitation of this study was its limited external validity arising from the single-center cohort design. Since the study was conducted exclusively at Chonburi Hospital, the findings may be subject to single-center bias, clinical protocols, and resource availability specific to this institution. Furthermore, the patient cohort may not fully represent the general population with pregnant women with GH due to geographic, socio-economic, or ethnic homogeneity within the center's catchment area. Consequently, the generalizability of these findings to other clinical settings or diverse populations remains uncertain. However, a significant strength of this study was an adequate sample size to answer the research question about incidence of preeclampsia progression in GH pregnancy. This study had picked up the interesting factors, DBP at the first time of GH diagnosis and prepregnancy BMI, that could be associated with progression of preeclampsia in GH pregnancy. Further studies focusing on this topic may be required.

## Conclusion

The findings of this study showed that pregnant women with GH had a higher risk of progressing to preeclampsia than the general pregnant population. This was reflected in an incidence of 25.7% in this study's cohort, which was approximately 3-5 times higher than in the general population<sup>(1)</sup>. This progression was associated with a significantly increased risk of adverse perinatal outcomes, including preterm birth, a higher rate of cesarean sections, and a lower neonatal birth weight. Another important finding was that an early diagnosis of GH and a higher DBP at diagnosis were significantly associated with the development of preeclampsia.

Thus, the patient who was diagnosed with GH prior to 34 weeks of gestation or those with a DBP

≥ 100 mmHg at diagnosis had a higher risk of progression to preeclampsia, especially at approximated 36 weeks of gestation. Consequently, counselling and close follow-up are required. A notable limitation of this research was its single-center cohort design, which resulted in a lack of population diversity. Therefore, further large-scale multicenter studies are recommended to confirm these findings and explore additional risk factors.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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