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# Thai Journal of Obstetrics and Gynaecology

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Improvement of TJOG has been documented. TJOG was accepted for indexing by the Thai Journal Citation Index (TCI) in December 2010 and indexed in the ASEAN Citation Index (ACI) in September 2015. TJOG also received the National Journal Award from the 3rd TCI-Scopus-TRF Journal Awards on December 15, 2016.

**Direction to contributors.** All papers should be sent to Editor, Thai Journal of Obstetrics and Gynaecology by online submission. The editorial board will decide upon the time of publication and retain the right to modify the style and the length of the contribution. However, major changes will be agreed with the authors.

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# Thai Journal of Obstetrics and Gynaecology

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# EDITORIAL

This fifth issue of Thai Journal of Obstetrics and Gynaecology 2022 contains many interesting articles. One special article is "Preconception care for obese women".

Editor in Chief and managing staff of the Thai Journal of Obstetrics and Gynecology already attended "System Development and Quality Improvement of Thai Journals in Scopus Database" on August 11, 2022 at Eastin Grand Hotel, Sathorn Road, Bangkok, Thailand. The objective is to develop and improve the quality of research articles of Thai journals in the Scopus database, as well as to create a profession editor's career path in Thailand. A new modern online submission system called Editorial Manager (EM) of Aries, a journal manuscript management system, has been implemented in Thailand's journals. It is also connected to the Publons database to invite experts to evaluate the quality of the manuscripts. The quality of Thai Journal of Obstetrics and Gynaecology is continuously rising.

The Royal Thai College of Obstetricians and Gynaecologiste (RTCOG) Annual Meeting 2022 will be held during 25-28 October 2022 at Pattaya Exhibition and Convention Hall (PEACH), Royal Cliff Beach Hotel, Chonburi, Thailand. The theme of this meeting is "**OBG62 Next Gen**". This meeting will have **AOFOG** session on the topic "**Current Controversies in O&G Practice"**. All RTCOG members are cordially invited to participate this scientific meeting.

Residents who would like to publish their researches in TJOG should submit their works before September 30, 2022. Our editorial team and constructive reviewers will let them know the results before December 31, 2022.

Wish to see you at RTCOG Annual Meeting 2022 at Pattaya Exhibition and Convention Hall (PEACH), Royal Cliff Beach Hotel, Chonburi, Thailand.

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

Thai Journal of Obstetrics and Gynaecology
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## SPECIAL ARTICLE

# Preconception Care for Obese Women

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**ABSTRACT**

Obese women increase adverse pregnancy outcomes when they get pregnant. Preconception care for obese women should be provided in order to plan for favorable pregnancy outcomes. The topics of preconception care include past history, personal history, family history, obstetric and gynecological history, and health promotion. Obese women should lose weight by 5-10%, have adequate exercise and have adequate nutrition especially folic acid before pregnancy. When pregnant, obese women should have appropriate weight gain.

**Keywords:** obesity, preconception, counseling, folic acid.

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Preconception care is defined as the process of providing biomedical, behavioral, and social health interventions to women and couples before conception occurs[1]. The objectives of preconception care are to reduce behavioral and individual and environmental factors that cause poor maternal and child health outcomes and to improve health status in both the short and long term of maternal and child health[1].

Obesity is defined as a body mass index of at least or more than 30 kg/m$^2$[2]. It can be classified into 3 classes (Table 1).

**Table 1.** Body mass index categories[2].

| Category | WHO body mass index (kg/m$^2$) |
|---|---|
| Underweight | < 18.5 |
| Normal weight | 18.5 - 24.9 |
| Overweight | 25 - 29.9 |
| Obesity class 1 | 30 - 34.9 |
| Obesity class 2 | 35 - 39.9 |
| Obesity class 3 | ≥ 40 |

Preconception care looks like the process of finding the diseases in sick patients. The process includes history taking, physical examination and laboratory investigations. At King Chulalongkorn Memorial Hospital, the laboratory

investigations for preconception care in general couples include blood group (ABO, Rh), complete blood count, syphilis (venereal disease research laboratory (VDRL) or chemiluminescent microparticle immunoassay (CMIA)), hepatitis B antigen and antibody, anti-human immunodeficiency virus (HIV), rubella IgG and hemoglobin typing. The laboratory investigations for preconception care in obese women should add investigations to finding the diseases, for example, fasting plasma glucose or hemoglobin A1c for finding diabetes mellitus.

Prepregnancy obesity increases the risk of preeclampsia, gestational hypertension (GHT), gestational diabetes mellitus (GDM), indicated and spontaneous preterm delivery, thromboembolic disease, cesarean section and fetal macrosomia. The incidence of pregnant women with obesity at King Chulalongkorn Memorial Hospital was 2.4, 5.5, 16.6, 12.6, 12.3 and 12.4% in 2016, 2017, 2018, 2019, 2020, and 2021, respectively[3].

**Timing for preconception care**

Preconception care should offer during the check-up period, on the occasion of negative pregnancy test and postpartum period or fourth trimester[4-6]. The postpartum period is a good time for postpartum care, proper contraceptive counseling, planning for the next pregnancy, and long-term health care[4, 5].

***Preconception care for obese women***

The Center for Diseases Control (CDC) has stratified topics in preconception care. The topics include health promotion, personal history, nutrition, immunizations, infectious diseases, medical conditions, exposures, and special populations[7].

Obese women should receive basic preconception care similar to all women but should pay attention to health promotion, previous surgery (previous cesarean section), medical conditions (DM, HT, cardiovascular disease, depression/anxiety, eating disorder), exposures (substances, medications), and disabilities[8].

The specific aim of preconception care for obese women is to provide education regarding the risks of adverse pregnancy outcomes while obese so that they can decide whether and when to get pregnant. They should know the complications of pregnancy increase with higher prepregnancy body mass index (BMI). They should be empowered to lose weight and have exercise before pregnancy in order to reduce the risk[8].

Like history taking, the topics for preconception care should include past history, personal history, family history, and obstetric and gynecological history. Health promotion topics should be also added (Table 2).

**Table 2.** Topics in preconception care (modified from[7]).

| |
|---|
| Past history |
| Medical conditions: diabetes mellitus, hypertension, cardiovascular disease, etc. |
| Infectious diseases: chlamydia, gonorrhea, HIV, syphilis, tuberculosis |
| Immunizations history: hepatitis B, HPV, measles, mumps, rubella tetanus, diphtheria, pertussis, varicella, COVID-19 |
| Previous surgery: previous cesarean section, bariatric surgery |
| Personal history |
| Alcohol, tobacco, illicit substances |
| Family history |
| Known genetic conditions |
| Obstetric and gynecological history |
| Previous miscarriage |
| Previous preterm birth |
| Previous stillbirth |
| Uterine anomalies |
| Health promotion |
| Family planning and reproductive life plan |
| Weight status |
| Exercise |
| Nutrient intake: folic acid, vitamin, calcium, iodine, essential fatty acids |

**Past history**

***• Medical conditions***

The general points for medical conditions include the pregnancy's effect on the medical conditions and the medical conditions' influence on the pregnancy course or the fetus. Some medical conditions that may worsen the pregnancy outcomes include treated or active cancer, previous peripartum cardiomyopathy, antiphospholipid antibodies, systemic lupus erythematosus and congenital heart disease[5].

Obesity is associated with various medical conditions such as DM, and HT. The risk of embryopathies from DM can be decreased by good glycemic control. Diabetic obese women should have good glycemic control before pregnancy. Obese women with diabetes should have regular exercise as it improves glycemic control in pregnant and nonpregnant women. Women with a BMI of > 25 kg/m$^2$ and 1 risk factor for DM should be screened for DM before pregnancy[9].

Obese women with longstanding HT should be evaluated for end-organ involvement. These include an echocardiogram to evaluate for left ventricular hypertrophy, serum creatinine and urine protein to evaluate renal disease, and an ophthalmologic study to evaluate the retina. They should be planned to change antihypertensive drugs. Some antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should not be used during pregnancy[8]. ACEIs can cause fetal malformations when used in the second and third trimesters. These include oligohydramnios, hypoclavaria, and renal dysfunction[5]. ARBs are presumed to have the same fetal effects as ACEIs[5].

Obese women may have eating disorders such as bulimia, and depression. They should undergo screening for eating disorders and depression[8].

*Diabetes mellitus*

DM is the prototype of a condition for which preconception counseling is beneficial. DM is an associated risk for adverse pregnancy outcomes. If a woman maintains glucose levels close to normal, many of these complications can be avoided before conception[5]. ACOG has concluded that preconception counseling for women with pregestational DM is beneficial and cost-effective and should be encouraged[10].

American Diabetic Association recommends preconception care for women with DM. the guidelines advise an inventory of disease duration and related complications and clinical and laboratory examination for end-organ damage. They encourage a preconceptional hemoglobin A1c level goal below 7%[11]. Hemoglobin A1c can also forecast the risks for gestational DM and for major anomalies[12].

A previous study found that preconception counseling improved hemoglobin A1c levels, folic acid compliance, and optimal pregnancy preparation[13]. Women with DM who undergo preconception counseling also have improved glycemic control before pregnancy and in the first trimester and experience lower rates of adverse pregnancy outcomes[14].

***• Infectious diseases***

Obese women should screen for infectious diseases before conception. Common infectious diseases that are usually screened are syphilis, viral hepatitis B, and HIV. If they had infectious diseases, they should receive treatment before pregnancy.

***• Immunizations history***

Preconception counseling for obese women, similar to non-obese women, should include an assessment of immunity against common pathogens. Other immunizations may be indicated depending on health status, travel plans, and time of year[5].

Live-virus vaccines are contraindicated during pregnancy. These vaccines include vaccines against varicella-zoster, mumps, measles, rubella, polio, chicken pox, and yellow fever. Conception should attempt 1 month or longer after live-virus vaccination[5].

With recent infections from COVID-19, obese women should receive the COVID-19 vaccine before or during pregnancy. COVID-19 vaccines are safe for fetus due to not live-virus vaccines[15].

Toxoid vaccines such as tetanus are suitable before and during pregnancy. Killed bacteria or viruses' vaccines are not associated with adverse fetal outcomes

and are suitable before and during pregnancy. These killed bacteria or viruses vaccines include vaccines against influenza, pneumococcus, hepatitis B, meningococcus, and rabies[5].

• ***Previous surgery***

*Previous cesarean section*

More than 50% of women with obesity will have cesarean sections, thus, a history of previous cesarean section must be identified. They should be advised to wait at least 18 months before pregnancy[8].

*Previous bariatric surgery*

Bariatric surgery is an option for women with class III obesity (BMI > 40 kg/m$^2$) or with class II obesity (BMI > 35 kg/m$^2$) with medical conditions. Maternal age is also an important aspect because the time to get pregnant should be delayed for a 6-month weight loss phase of medical management and at least a 6-month postoperative phase after bariatric surgery. Women should also screen for medical conditions that are commonly associated with obesity, such as DM, HT, obstructive sleep apnea, and depression[8].

Obese women should receive contraceptive counseling and should be informed that conception should be delayed in the initial phase of rapid weight loss (within the first postoperative year after bariatric surgery) before performing bariatric surgery. This time will ensure adequate healing time and maximize weight loss. Obese women may have a higher risk for malnutrition and small-for-gestational-age (SGA) infants when they become pregnant during the period of rapid weight loss. However, the benefits of bariatric surgery are the improvement of reproductive functions such as anovulation and polycystic ovarian syndrome and increased fertility rates[8].

Weight loss before pregnancy is the single effective intervention to decrease medical conditions, especially DM and HT[16]. Previous studies found that bariatric surgery decreased risks of shorter gestation, GDM and excess fetal growth. But, bariatric surgery increased the risk of SGA infants, and possibly increased mortality[17, 18].

Obese women who have a history of bariatric surgery increase risk for nutritional deficiencies, especially with a history of diverting surgery. Obese women who have a history of a Roux-en-Y surgery should be evaluated for folate, calcium, vitamin B12, protein, and iron deficiency anemia. When they get pregnant, they should be monitored for fetal growth with an obstetric ultrasonogram during pregnancy[8].

## Family history

• ***Known genetic conditions***

*Thalassemia*

Thalassemia is a common single gene disorder that have disorders of globin chain synthesis. There have at least 200 million people who carry a gene for one of these hemoglobinopathies and hundreds of known mutations to cause thalassemia syndromes. The endemic areas include the Mediterranean and Southeast Asian countries. Obese women and couples in endemic areas should undergo thalassemia carrier screening. If they are the couple at risk for thalassemia syndromes, they should receive genetic counseling for preimplantation diagnosis, prenatal diagnosis and pregnancy outcomes[5, 19].

*Neural tube defects*

The incidence of neural tube defects (NTDs) is 0.9 per 1,000 live births. They are the second most frequent structural fetal malformation. Some of NTDs are associated with gene mutations. Mutation of methylenetetrahydrofolate reductase gene (677C → T substitution) is one location associated with NTDs[5].

A previous trial found that periconceptional folic acid treatment significantly reduced the risk for a recurrent NTDs by 72%[20]. One study also demonstrated that universal folic acid supplementation reduced the priori risk of a first NTDs[21]. Thus, all women who may become pregnant are recommended to take 400-800 micrograms/day of folic acid orally before conception and through the first trimester[22].

## Health promotion

• ***Family planning and reproductive life plan***

Obese women aged 35 years or older have to weigh the risks of delayed pregnancy and advancing

maternal age on aneuploidy and fertility function compared with pregnancy at the current weight. Obese women aged less than 35 years are advised to have a target weight loss for up to one year before pregnancy. Obstetricians should consider the women's age, obstetrics and gynecological history, and the intended family size when planning a prepregnancy weight loss program[8].

• ***Weight status***

Obesity has many health problems. These health problems include HT, DM, coronary artery disease and sleep disorders. Obesity also has effects on reproduction by reducing fecundity and fertility[8].

Prepregnancy obesity increases the risk of preeclampsia, GHT, GDM, thromboembolic disease, preterm delivery, cesarean section and fetal macrosomia[23-25]. It is essential to inform these adverse pregnancy outcomes for preconception care for women with obesity. The risk for most adverse pregnancy outcomes occurs at a BMI of 35 kg/m$^2$. A previous study found that some pregnancy outcomes can be improved with a modest decrease in weight[26].

Obese women are at increased risk of pregnancies affected by congenital malformations. These congenital malformations included NTDs (odds ratio (OR) 1.87, 95% confidence interval (CI) 1.62-2.15), hydrocephalus (OR 1.68, 95% CI 1.19-2.36), limb reduction (OR 1.34, 95% CI, 1.03-1.73), cardiac defects (OR 1.30, 95% CI, 1.12-1.51), and cleft lip & palate (OR 1.20, 95% CI, 1.03-1.40) (Table 3)[27]. Obese women are also at increased risk of fetal demise. The risk for stillbirth is 2.1-4.3 fold higher in obese women when compared with normal-weight women[27].

**Table 3.** Congenital malformations in obese versus non-obese pregnant women[27].

| congenital malformations | odds ratio | 95% confidence interval |
|---|---|---|
| neural tube defects | 1.87 | 1.62 - 2.15 |
| hydrocephalus | 1.68 | 1.19 - 2.36 |
| limb reduction | 1.34 | 1.03 - 1.73 |
| cardiac defects | 1.30 | 1.12 - 1.51 |
| cleft lip & palate | 1.20 | 1.03 - 1.40 |

A previous study demonstrated the risks of adverse pregancy outcomes by BMI group. Adverse outcomes included preeclampsia, shoulder dystocia, cesarean section, large for gestational age, birth weight > 4,500 g, stillbirth > 28 weeks and early neonatal death. All adverse outcomes increased when BMI increased[28]. Data from the United States confirmed an increased risk of cesarean section. In nulliparous women without medical conditions, the cesarean section rate was 11.4% among underweight women and increase to 42.6% in women with class III obesity (BMI > 40 kg/m$^2$). When all women were included, the cesarean rate was 40.3% in women with class III obesity (BMI > 40 kg/m$^2$) without risk factors, but increase to 49.2% in those with preexisting DM or GDM, 43.8% with chronic HT, and 58.8% with both HT and DM[29].

A previous study by Schummers et al found that modest differences in BMI were associated with a decrease in adverse pregnancy outcomes. They demonstrated that a 10% decrease in prepregnancy BMI could decrease the risk of indicated preterm birth, GDM, preeclampsia, stillbirth and macrosomia by at least 10%. These data also reveal that 20-30% differences in prepregnancy BMI would be needed to see a change in rates of shoulder dystocia, cesarean section, 48-hour neonatal intensive care unit (NICU) stay, and newborn mortality[26].

Some adverse pregnancy outcomes associated with obesity increase during pregnancy when excessive weight gain occurs. Thus, appropriate weight gain during pregnancy should be counseled preconception because excess weight gain increases the maternal risk of complications (DM, preeclampsia, operative delivery) and increase the risk of childhood obesity.

This confirms the importance of setting ideal gestational weight gain[8]. The recommendations for ideal gestational weight gain by prepregnancy BMI are shown in Table 4.

**Table 4.** Recommendations for total and rate of gestational weight gain by prepregnancy BMI[30].

| Prepregnancy BMI | BMI (kg/m$^2$) (WHO) | Total weight gain range (kgs) | Rates of weight gain 2$^{nd}$ and 3$^{rd}$ Trimester (Mean range in kgs/wk) |
|---|---|---|---|
| Underweight | < 18.5 | 12.5 - 18.0 | 0.51 (0.44 - 0.58) |
| Normal weight | 18.5 - 24.9 | 11.5 - 16.0 | 0.42 (0.35 - 0.50) |
| Overweight | 25.0 - 29.9 | 7.0 - 11.5 | 0.28 (0.23 - 0.33) |
| Obese (includes all classes) | ≥ 30.0 | 5.0 - 9.0 | 0.22 (0.18 - 0.27) |

From this information, obese women should lose weight before pregnancy. Counseling regarding diet and exercise with a focus on lifestyle and behavior modification will be sufficient for some women with obesity. Obese women should be informed to set appropriate weight loss goals before conception and emphasis optimizing health. Multimodal interventions include lifestyle modifications in diet, exercise, and behavioral change should be used to lose weight[8]. Planning a target weight loss of 5-10% is appropriate (4.5-11 kgs) for women with class II obesity (BMI > 35 kg/m$^2$). If this is achieved, it would decrease 1 BMI class. In addition, women with class III obesity (BMI of > 40 kg/m$^2$) or > 35 kg/m$^2$ with medical conditions should have the option of bariatric surgery[8].

• ***Exercise***

A previous study found that only 5% of participants have an exercise for 30 minutes per day[31]. Thus, women should be encouraged to have a target of 150 minutes of moderate exercise per week or 75 minutes of vigorous exercise per week and also have muscle-strengthening activities at least 2 days per week[32].

The current recommendation suggests that all pregnant women without contraindications to exercise should have at least 30 minutes per day of moderate-intensity exercise. The study demonstrates that exercise can limit weight gain and improve glucose tolerance in pregnant women with obesity[33].

• ***Nutrient intake and folic acid***

Obese women increase the risk of inadequate nutrient intake. Prenatal vitamins can alleviate some risks. Thus, an intake of calcium (1,000 mg/day) is recommended, either 3 times a day or once a day. Women with previous bariatric surgery, should be advised to have adequate levels of iron, folate, vitamin B12, and vitamin D. Vitamin A intake should be limited to 10,000 IU/day[8].

One previous meta-analysis found an increased OR for NTD in obese women (OR 1.70, 95% CI 1.34-2.15) and severely obese women (OR 3.11, 95% CI 1.75-5.46)[34]. A previous study in Thailand found that preconception folic supplementation was used in only 9.7%[35]. Epidemiologic studies also dea monstrated that obese women are less likely to have adequate folic acid or use nutritional supplements than normal-weight women[36]. Thus, the current recommendations are that women should receive standard folic acid supplementation of 400 micrograms per day before conception until 12 weeks of gestation and folic acid of 4 mg per day in women who have had an NTD-affected pregnancy. But the Royal College of Obstetricians and Gynaecologists (RCOG) recommends folic acid supplementation 5 mg per day for obese women[37].

## Conclusion

In conclusion, obese women are associated

with adverse pregnancy outcomes when pregnant. Preconception care should be provided regarding the risks of adverse pregnancy outcomes while obese so that they can decide whether and when to get pregnant. They should know those complications of pregnancy increase when BMI increases and be empowered to reduce the risk by exercising and losing weight before pregnancy.

## Potential conflicts of interest

The author declares no conflicts of interest.

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## OBSTETRICS

# Evaluation of Repeated Antenatal Blood Testing for Anemia, Human Immunodeficiency Virus, and Syphilitic Infection Screening during the Third Trimester: A single-center university hospital setting

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## ABSTRACT

**Objectives:** To compare first and repeated antenatal blood tests for screening anemia, human immunodeficiency virus (HIV), and syphilis serology status. Factors influencing maternal anemia were also evaluated utilizing multivariate analysis.

**Materials and Methods:** A prospective descriptive study involved 1,089 pregnant women who attended an antenatal care unit in a university hospital setting. Participants were asked to fill in a questionnaire. Blood tests at the first antenatal visit and again during the third trimester, approximately 12 weeks apart, were performed routinely (in all women). An analysis was performed to compare the results from both blood sampling periods.

**Results:** Hemoglobin and hematocrit levels were found to be significantly lower in the third trimester (first vs. third trimester; hemoglobin 12.2 ± 1.2 vs. 11.9 ± 1.2 g/dL, hematocrit 36.6 ± 3.5% vs. 36.1 ± 3.3%, $p < 0.001$). The incidence of anemia was 14.9% and 23.9% in the first and second laboratory tests, respectively ($p < 0.001$). Anemia diagnosed in the first trimester (odds ratio (OR) 5.46, 95% confidence interval (CI) 3.74–7.57), maternal underweight (OR 1.59, 95%CI 1.02–2.49), and poor compliance (OR 2.56, 95%CI 1.25–5.21) with ferrous supplementation were considered significant risk factors for anemic status being observed in the third trimester. The prevalence of HIV and syphilis infection were 3.6/1,000 and 1.8/1,000, respectively. Four syphilis seroconversions were observed in which 2 of these 4 were subsequently confirmed as syphilis infection by specific Treponemal test (0.2%). There was no HIV seroconversion in the study population.

**Conclusion:** A significant decrease in hemoglobin and hematocrit levels warrants the need for a repeated complete blood count in the late trimester. Patients with risk factors, including i) first trimester diagnosis with anemia, ii) low body weight, and iii) poor compliance with taking antenatal supplements, require close monitoring to alleviate the severity of anemia at delivery. Due to a 0.2% seroconversion rate of syphilitic infection, the authors recommend repeat syphilitic serologic testing regardless of the sexual transmitted infection risks. Despite a high prevalence of HIV

infection, absent of seroconversion in the study population warrants re-consideration of universal repeated screening of HIV infection in the third trimester. Further cost-utilization studies are required to draw conclusion regarding repeated serologic screening blood tests.

**Keywords:** anemia, HIV, repeated blood test, seroconversion, syphilis, pregnancy.

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# *การวิเคราะห์ผลของการตรวจเลือดฝากครรภ์ซ้ำในไตรมาสที่ 2 หรือ 3, งานวิจัยสถาบันเดี่ยวในโรงพยาบาลมหาวิทยาลัย*

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## *บทคัดย่อ*

***วัตถุประสงค์****: การวิจัยศึกษาเปรียบเทียบการตรวจเลือดในการฝากครรภ์ครั้งแรก และการตรวจเลือดซ้ำในไตรมาสที่สาม ได้แก่ ตรวจประเมินภาวะซีด ตรวจการติดเชื้อเอดส์ และการติดเชื้อซิฟิลิส ร่วมกับเก็บข้อมูลปัจจัยที่มีผลให้เกิดภาวะซีดในหญิงตั้งครรภ์*

***วัสดุและวิธีการ****: หญิงตั้งครรภ์จำนวน 1,089 คน ได้รับการฝากครรภ์ที่โรงพยาบาล เข้าร่วมวิจัยโดยตอบแบบสอบถาม และทบทวนเวชระเบียน*

***ผลการศึกษา****: หญิงตั้งครรภ์ในงานวิจัย 1,089 คน พบว่ามีระดับฮีโมโกลบิน และฮีมาโตคริดลดลงอย่างมีนัยสำคัญในไตรมาสที่สาม โดยเข้าเกณฑ์วินิจฉัยภาวะซีดในหญิงตั้งครรภ์จากการตรวจเลือดในการฝากครรภ์ครั้งแรก และจากการตรวจเลือดในไตรมาสที่สามคิดเป็นร้อยละ 14.9 และ 23.9 ตามลำดับ ปัจจัยที่มีผลต่อภาวะซีดในไตรมาสที่สามคือ ตรวจพบภาวะซีดในการตรวจเลือดครั้งแรก, ภาวะน้ำหนักน้อยกว่าเกณฑ์, และการรับประทานธาตุเหล็กเสริมอย่างไม่สม่ำเสมอ นอกจากนี้พบการติดเชื้อเอดส์คิดเป็นร้อยละ 0.36 โดยไม่พบการติดเชื้อเพิ่มในการตรวจเลือดในไตรมาสที่สาม ส่วนการติดเชื้อซิฟิลิสพบร้อยละ 0.18 และพบการติดเชื้อเพิ่มในการตรวจเลือดในไตรมาสที่สามจำนวน 2 ราย*

***สรุป****: ผู้นิพนธ์สนับสนุนการตรวจเลือดเพื่อประเมินภาวะซีดซ้ำในไตรมาสที่สาม โดยเฉพาะหญิงตั้งครรภ์ที่มีปัจจัยเสี่ยงดังผลการวิจัยข้างต้น และควรได้รับการเฝ้าระวังภาวะแทรกซ้อนจากภาวะซีดในช่วงคลอด นอกจากนี้ พบผู้ติดเชื้อซิฟิลิสเพิ่มในการตรวจเลือดซ้ำร้อยละ 0.2 ผู้นิพนธ์จึงสนับสนุนการตรวจเลือดซ้ำเพื่อวินิจฉัยการติดเชื้อซิฟิลิส หญิงตั้งครรภ์ที่ติดเชื้อเอดส์ในงานวิจัยมีอุบัติการณ์สูงในประชากร แต่ไม่พบการติดเชื้อเพิ่มในการตรวจเลือดซ้ำ ผู้นิพนธ์เห็นว่าควรพิจารณาอย่างถี่ถ้วนในการส่งตรวจการติดเชื้อเอดส์ซ้ำในหญิงตั้งครรภ์ทุกราย*

***คำสำคัญ****: โลหิตจาง, เอชไอวี, การตรวจเลือดซ้ำ, ผลเลือดเปลี่ยนแปลง, ซิฟิลิส, หญิงตั้งครรภ์*

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## Introduction

The ultimate goal of pregnancy care is health and safety of both the mother and the newborn baby. In order to achieve this goal, antenatal care plays an important role. The risks to individual woman can be recognized by taking their history, physical examination, and performing certain investigations, including blood tests, to guide an obstetrician and healthcare team for proper patient management both during the antenatal and the intrapartum period. Prenatal blood screening for common diseases, such as anemia, thalassemia, and serious sexual transmitted infections (STIs), is universally performed during the patient's first visit. Abnormal results obtained can subsequently allow the physician to provide proper counseling and further management to prevent maternal and fetal morbidity/mortality.

The Royal Thai Collage of Obstetricians and Gynecologists (RTCOG) guideline for the first prenatal blood test is a modified version of the international guideline. The World Health Organization (WHO) recommendation for prenatal blood tests includes: i) either hemoglobin/hematocrit level or complete blood count (CBC), ii) Rh blood typing, and iii) syphilis, human immunodeficiency virus (HIV), and viral serologic screening relevant to the individual setting of each hospital[1]. Thalassemia screening, ABO blood typing, and hepatitis B serologic test were added into the RTCOG version according to the considered high prevalence of thalassemia diseases and hepatitis B carriers among the Thai population. Nonetheless, there is growing evidence suggesting that a single blood investigation may be insufficient. Anemia is common during the late trimester. Patients can also contract HIV and syphilis at any time during pregnancy if they remain sexually active. Evidence suggests that repeated serologic screening for both HIV and syphilis should be offered but only for women in high-risk populations[2,3]. The detection of anemia as well as HIV and syphilitic seroconversion allows a proper care plan and patient management to be implemented to prevent future complications.

The RTCOG also published a guideline in 2011 suggesting that a repeated blood test for assessing the hemoglobin or hematocrit level, HIV, and syphilis serology should be done in all Thai pregnant women. Despite both evidence and the RTCOG recommendation, a significant number of hospitals and antenatal clinics still only conduct a single antenatal blood test policy. HRH Maha Chakri Sirindhorn Medical Centre (MSMC) is a university hospital situated in a suburban area of Thailand, 70 km from the capital Bangkok. The hospital antenatal clinic serves approximately 1,400 antenatal care per month. Before 2015, a blood test was performed once only in the first prenatal visit, and thus it was unable to estimate the rates of seroconversion and new cases of anemia that arose in the second half of pregnancy. This protocol has been cautiously revised according to the RTCOG guideline since 2015 to include performing a repeated blood test in the third trimester. In previous years, the proportion of teenage pregnancies in our area had been reported to be slightly high at 7.7%, with these considered a high risk group, and so the number of malnourished and anemic patients was expected to increase in our population, especially in the late trimester. In 2015, the hospital prevalence of HIV and syphilis in pregnancy were reported to be approximately 5/1,000 and 1/1,000, respectively. Such data define this as an endemic area for HIV infection[4]. It has been demonstrated that repeated HIV screening is a cost-effective strategy for the prevention of the perinatal transmission of HIV, even in a resource-limited country[5]. Hence, it would be worthwhile to evaluate whether repeated serology screening in the third trimester is necessary in our local setting.

The primary objective of the present study was to evaluate the utility of repeated antenatal blood tests in regards to detection of anemic status, through CBC values, and seroconversion of both syphilis and HIV in the third trimester as compared to the first prenatal visit. The factors influencing these changes were also determined utilizing multivariate analysis. The knowledge obtained from this study can facilitate policy modification in order to tackle these common antenatal care problems.

## Materials and Methods

This study was a prospective descriptive study conducted to evaluate the current antenatal intervention, i.e., the repeated blood sampling scheme, during the period between January 2016 and December 2016. All women having antenatal care at the MSMC were asked to participate the study when they visited the MSMC for the repeated blood test at the clinic. Only singleton pregnant women with neither fetal anomaly nor maternal hematologic diseases affecting either their red cell count or platelet concentration other than thalassemia (and hemoglobinopathy) were included in the study. All participants received standard dose of iron supplement, 200 mg of ferrous fumarate (approximately 66 mg of elemental iron) daily starting at 16-20 weeks once the patients were clear from morning sickness symptoms. In addition, women with a history of blood and other components' transfusion were not eligible for the study. All the participants had received their first antenatal blood test at either the MSMC or at other clinics according to the standard practice. The repeated blood test was performed at either 28-32 weeks gestation or at least 8 weeks following the first blood sampling if they had started their booking late. Nonetheless, if the first blood test had been done in the third trimester and it was not possible to achieve an 8-week interval for the blood sampling, the repeated blood test was performed in the labor ward just before delivery. All the pregnant women received pre-test counseling and had to give their voluntarily consent prior to the test according to the standard practice guideline. A questionnaire regarding the patient's demographic data and the factors associated with anemia and seroconversion was given to the patient following their written informed consent.

The repeated blood test included CBC, Anti-HIV, and Venereal Disease Research Laboratory test (VDRL) according to the RTCOG recommendation. Participants who had their first blood test positive for either Anti-HIV or VDRL were not tested again for the respective positive test, but their data were still included in the other analyses. Anemia was defined, according to the Centers for Disease Control and Prevention (1998), as when the hemoglobin level falls below 11 g/dL (hematocrit level falls below 33%) in the first and third trimesters[6]. The study received ethical approval from the Institutional Review Board (IRB) and was funded by the Faculty's Routine to Research (R2R) funding scheme.

### *Statistical analysis*

According to the primary outcome, in order to detect statistical significance with expected a 20% shift from a positive outcome (anemia) to negative and a 10% shift from negative to positive, with type I and II errors of 0.05 and 0.2, respectively; a total of 244 participants with both first and repeated blood test results were required. Nonetheless, the author wanted to evaluate the seroconversion incidence, especially for Anti-HIV, in which at least an incidence of 1/1,000 newly diagnosed Anti-HIV positive is considered an endemic area. Therefore, such a study would need to enroll at least 1,000 participants.

The demographic and outcome data were reported herein as either the mean ± standard deviation (SD) or proportion as appropriate. A significant difference in the hematocrit level, hemoglobin level, and platelet concentration between the first and repeated blood sampling tests was determined using the paired t test. The proportions of patients diagnosed with anemia were compared using McNemar's chi square test. Multivariate logistic regression analysis was used to identify the factors affecting the patient anemic status during the third trimester as a dependent variable, while the patient's age, body weight, educational background, income, parity, iron intake, iron supplementation, and a previous diagnosis of anemia as independent variables were fitted into the model using a backward elimination approach. The odds ratio (OR) with a 95% confidence interval (CI) was calculated. It was expected that the seroconversion rate of either the Anti-HIV or VDRL result would not be common, and therefore, only descriptive analysis would be used. A p value $< 0.05$ was determined to be statistically significant.

## Results

During a one-year period between January 2016 and December 2016, a total of 1,089 women with singleton pregnancy who were having antenatal care at the MSMC were enrolled into the study. Mean ± SD age and BMI of the participants were 28 ± 6.3 years old and 26.7 ± 4.8 kg/m$^2$, respectively. Approximately half (48.6%) were primigravida participants. The prevalence of teenage pregnancy (aged under 20 years old) and advanced maternal age (aged over 35 years old) were 10% and 17%, respectively. Only 1% of the participants were underweight (BMI < 18.5 kg/m$^2$), while approximately 40% of participants were overweight (BMI = 25.0 - 29.9 kg/m$^2$) and 20% were obese (BMI ≥ 30 kg/m$^2$) among the total number of women participating in the study. More than 75% had commenced their antenatal care earlier than 14 weeks of gestation (considered early antenatal care). The participants' occupational backgrounds are summarized in Table 1.

**Table 1.** Demographic data of the study population.

| | Demographic data | Proportion |
|---|---|---|
| Age group | Teenage | 10.0% |
| | 20 – 35 years | 72.9% |
| | Elderly | 17.1% |
| Weight | Underweight | 1.0% |
| | Normal | 39.2% |
| | Overweight | 39.3% |
| | Obese | 20.5% |
| Education | Lower than bachelor's degree | 67.6% |
| | Bachelor's degree | 32.4% |
| Income | Low | 5.6% |
| | Normal | 68.9% |
| | High | 25.5% |
| Occupation | Unemployed/housewife | 28.8% |
| | In agriculture | 2.9% |
| | Office worker | 11.6% |
| | Privately owned business | 34.7% |
| | Others or unclassified | 22.0% |
| Gravidity | Nulliparous | 48.9% |
| | Multiparous | 50.5% |
| | Grand multiparous (> 4) | 0.6% |
| Antenatal care | Late first antenatal care (> 14 weeks) | 23.7% |
| | First antenatal care < 14 weeks | 76.3% |
| Thalassemia screen | Normal | 64.8% |
| | Positive screening for thalassemia trait/disease | 17.1% |
| | Doubtful results | 18.1% |

Over one quarter of the participants were either unemployed or a housewife, while the majority were currently working in either the commercial or industrial sector, with only 3% employed in the agricultural sector. Approximately two-thirds of the participants had an educational background lower than a bachelor's degree. Nonetheless, almost 95% had an annual income of more than 60,000 baht (25.5% had a considered high annual income of more than 240,000 baht), leaving only 5.6% who had an income of less than 60,000 baht/year.

All the participants underwent a repeated blood test at the MSMC, comprising 43.6% who underwent their first blood test in an external clinic/health center and the other 56.4% who initially started their antenatal care at the MSMC. The majority (64.8%) of the participants were found to be negative (normal) for thalassemia in the screening performed either by the MSMC or as part of the national (Ministry of Public Health) screening program. Approximately 17.1% of the study population were diagnosed with a thalassemia trait, primarily the hemoglobin E trait/disease and beta-thalassemia trait, respectively. Another 18.2% were suspected to have a thalassemia trait without diagnostic confirmation. This group of participants were couples without a risk of severe fetal thalassemia diseases according to the couple screening program. Overall, both hemoglobin and hematocrit levels were significant lower in the third trimester testing when compared to the first antenatal care visit, as shown in the Table 2 (first vs. repeated blood test; hemoglobin 12.2 ± 1.2 vs. 11.9 ± 1.2 g/dL, hematocrit 36.6 ± 3.5 vs. 36.1 ± 3.3%, $p < 0.001$).

**Table 2.** Comparison of the hemoglobin level, hematocrit level, platelet count and anemic status between the first and repeated antenatal test.

| Demographic data | First blood test† | Repeated blood test | p value* |
|---|---|---|---|
| Hemoglobin (g/dl) | 12.2 (1.2) | 11.9 (1.2) | < 0.001 |
| Hematocrit (%) | 36.6 (3.5) | 36.1 (3.3) | < 0.001 |
| Women diagnosed with anemia‡ , n (%) | 162 (14.9%) | 260 (23.9%) | < 0.001 |
| Platelet count | 301,425 (62,314.7) | 268,955 (62,781.4) | < 0.001 |
| Positive Anti-HIV serologic status, n (%) | 4/1,088 (0.36%)¶ | 0/1,084 (0%)§ | - |
| Positive syphilitic infection, n (%) | 2/1,088 (0.18%)¶ | 2/1,086 (0.18%)§ | - |

Data are presented as mean (SD)

† Mean (SD) gestational age at first ANC = 11 (5.2) weeks.

* Student t-test for mean differences & chi-square test for proportional data.

‡ Defined by the WHO criteria[6] - see text

¶ Prevalence at first antenatal blood test

§ Incidence of sero-conversion at the second blood test

The incidences of anemia, according to the WHO criteria, were significantly higher at the second laboratory test (third trimester) time-point (14.9% vs. 23.9%, $p < 0.001$). Similarly, the mean platelet count in the repeated blood test was significantly lower than the first ANC result (mean difference, - 31,816 ± 52,332, $p < 0.001$).

In order to identify the key risk factors influencing the diagnosis of anemia in the third trimester, log regression analysis (both univariate and multivariate) was performed. Body composure, compliance with taking ferrous supplementation, and diagnosis of anemia during the first trimester were considered to be the determining factors for anemia in the third trimester. Patients diagnosed with anemia in the first trimester were approximately 5.5 times more likely to be anemic in the third trimester (multivariate analysis: adjusted OR 5.46, 95%CI 3.74-7.97, $p < 0.001$). Underweight patients

had a 1.6 times higher chance to be diagnosed with anemia during the third trimester (adjusted OR 1.59, 95%CI 1.02-2.49, p < 0.05). Also, they were approximately 1.5-2.5 times more likely to be diagnosed with anemia in the late trimester if the patients did not take ferrous supplementation regularly (adjusted OR 1.54 and 2.56 in less and poor compliance patients, respectively, p < 0.05). Other factors collected from the study questionnaire that were included in the multivariate analysis are shown in Table 3.

**Table 3.** Multivariate logistic regression analysis[δ] regarding the risk factors influencing maternal anemia in the third trimester (repeated blood test).

| Factor | Adjusted OR | 95%CI | p value |
|---|---|---|---|
| Age group | | | 0.06 |
| Teenage pregnancy | 1.04 | 0.60-1.81 | 0.88 |
| Elderly gravidarum | 0.66 | 0.42-1.05 | 0.08 |
| Body weight | | | < 0.01 |
| Underweight | 1.59 | 1.02-2.49 | < 0.05 |
| Overweight | 0.70 | 0.13-3.76 | 0.68 |
| Obesity | 1.22 | 0.78-1.92 | 0.38 |
| Lower educational background | 0.92 | 0.64-1.32 | 0.65 |
| Income | | | 0.13 |
| Low income | 1.59 | 0.84-3.03 | 0.16 |
| High income | 0.94 | 0.64-1.39 | 0.76 |
| Parity | | | 0.59 |
| Multiparous | 1.26 | 0.90-1.76 | 0.18 |
| Grand multiparous | 1.11 | 0.17-7.15 | 0.91 |
| Reduced-ferrous diet[†] | 0.72 | 0.51-1.03 | 0.07 |
| Ferrous supplementation | | | < 0.01 |
| Less compliance (sometimes take) | 1.54 | 1.07-2.22 | < 0.05 |
| Poor compliance (seldom take) | 2.56 | 1.25-5.21 | < 0.05 |
| No compliance (never take)[‡] | 1.61 | 0.37-7.03 | 0.53 |
| Previous diagnosed anemia (first visit) | 5.46 | 3.74-7.97 | < 0.001 |

OR: odds ratio, CI: confidence interval

[δ] Factors included in the model were age, body mass index, educational background, income, and parity as fixed variables, while reduced ferrous diet, compliance with ferrous supplementation, abnormal glucose tolerance, aspirin prescription, hometown region, history of postpartum hemorrhage, and history of low birth weight were the tested variables.

[†] Reduced ferrous diets include i) vegetarian diet, ii) meat, internals, green leaf, or egg abstention.

[‡] n = 10.

Concerning the serologic results, the prevalence of HIV and syphilis infections were 3.6/1,000 and 1.8/1,000, respectively. Overall, proportions of women with risk factors of HIV, syphilis and STIs (including cervicitis, pelvic inflammatory diseases, condyloma) in the study population were multiple partners 20.8%, history of STIs 1.5% and history of illicit drugs used 5.8%, respectively. There were 4 new positive syphilis

screening results in the second laboratory tests, in which 2 of these 4 were confirmed as syphilis infection by Treponemal and non-Treponemal specific tests. The first patient, 24 years old and nulliparous, had no syphilis screening during the first trimester. The second patient, 35 years old and nulliparous, was a housewife and had no history of either multi-partners or a previous STD. She only had a poor income of less than 60,000 baht annually. The other 2 women were confirmed with false-positive syphilis screening by showing negative Treponemal test. Regarding the HIV blood test, there was no seroconversion observed in the study population. We did not repeat the test for hepatitis B surface antigen (HBsAg) in the third trimester, while the prevalence from the first antenatal blood test was 2.8% (30/1,089).

## Discussion

Overall, the study demonstrated a statistically significant decrease in both hemoglobin (mean difference 0.4 ± 1.1 mg/dL, 95%CI 0.3-0.5, $p < 0.001$) and hematocrit (mean difference 0.5 ± 3.3%, 95%CI 0.3-0.7, $p < 0.001$) levels in the third trimester when compared to the first visit antenatal blood test. Anemia diagnosed at the first visit was the strongest determinant factor influencing maternal anemia in the late trimester, while a patient's BMI and compliance with taking ferrous supplementation were also associated with the diagnosis of anemia in the late trimester. The prevalence of HIV infection in pregnancy was 3.6/1,000 without new seroconversion observed in the study population. The prevalence of syphilis infection was observed to be 1.8/1,000, but there were 2 cases of seroconversion found in the repeated blood tests.

Hypervolemia is a physiologic change that occurs from the beginning of pregnancy and progresses until delivery. For example, the plasma volume expansion is around 14% at 12 weeks gestation[7] and increases to a maximum of around 40–45% after 32–34 weeks[8]. However, there is a discrepancy between the increases in both components in which the plasma volume extension is more than the increase in the red cell volume. Consequently, hemoglobin and hematocrit concentrations slowly decline, but the hemoglobin should not drop lower than 10.5 g/dL (hematocrit < 32%) in the mid-trimester and 11.0 g/dL (hematocrit < 33%) in the first and third trimester. These numbers are used as cut-off values for diagnosing anemia in pregnancy[6]. In our study population, a decrease in both hemoglobin (-0.4 ± 1.1 mg/dL, 95%CI 0.3-0.5, $p < 0.001$) and hematocrit (-0.5 ± 3.3%, 95%CI 0.3-0.7, $p < 0.001$) levels, and platelets concentration in the late trimester could be theoretically explained by a dilution effect. However, the dilution effect cannot cause adverse outcomes if anemia is not diagnosed.

In 2011, the World Health Organization (WHO) reported that the prevalence of anemia in women of reproductive age (15-49 years old), who are eligible to get pregnant, and in pregnant women were 19.9% and 24.5%, respectively[9]. Compared to the WHO study, this study found the prevalence of anemia in pregnancy at 14.9% and 23.9% as observed at the first and repeated antenatal blood tests, respectively. The prevalence of anemia varies among regions and countries. A study in China by Zhao and colleagues demonstrated the prevalence of anemia in pregnancy during 2012-2016 were 10.1%, 26.7%, and 28.1% in the first, second, and third trimester, respectively[10]. Whereas a systematic review performed in Nigeria observed 25-45.6% of iron deficiency anemia in the pregnant population[11]. Policies regarding blood tests for anemia are, therefore, different from country to country. For example, a retrospective study in Austria observed proportions of anemia diagnosed during the first (< 16 weeks) and second (third trimester) to be 2.2% and 13%, respectively. The Austrian authority then concluded that the first examination is not mandatory for antenatal care[12]. Our finding regarding anemia prevalence and its increase during the late trimester did not against implementation of the repeated blood tests scheme. The authors suggest that each institution should evaluate own population and adjust the policy accordingly.

Previous diagnosis with anemia detected from the first prenatal visit was the greatest predictive factor for a diagnosis of anemia in the late trimester. Moreover, pregnant women who were malnourished as indicated by a low pre-pregnancy BMI (< 18.5 kg/m$^2$) had a higher chance to be anemic in the third trimester. Poor compliance with taking ferrous supplementation

regularly also increased the risk of anemia later during the gestational period. This can imply that in the study population a patient's nutritional status was a major determining factor of anemia in pregnancy, and this was similar to what has been previously described in the literature. In Pakistan, as another Asian population, specific types of food consumption, such as pica, tea, and a low intake of eggs and red meat were associated with anemia in an urban area[13]. Another study involving a Portuguese population reported that being a teenager was the only risk factor of iron storage depletion[14]. A systematic review from the Nigerian group observed that multiparity and low socioeconomic status, or just being in the third trimester were risk factors for iron deficiency anemia. Moreover, factors associated poor compliance to routine iron therapy included poor utilization of antenatal services, low educational attainment, long distance to healthcare facility, being single, and teenage pregnancy[15]. A multivariate analysis study performed in Ghana, which observed a high prevalence of over 50% with anemia in pregnancy, demonstrated that poor dietary intake was associated with a 2.7-time increase of anemia (adjusted OR 2.73, 95%CI 1.35-5.50). Other associate risk factors were young maternal age, fewer antenatal contacts, and low BMI[16]. Therefore, pregnant women who are at risk for undernourished dietary status, i.e., low BMI observed in our study, teenage pregnant and lesser socioeconomic status found in other reports, should be identified during the antenatal care. Nutritional support - enriched ferrous diet, and iron supplement therapy should then be provided with scheduled repeated blood tests in the late trimester. However, we could not demonstrate the effect of teenage pregnancy in our study. This may be because our institution has a robust health education program for teenager (to be) mothers during the antenatal care. Henceforth, the nutritional status was observed to be a distinctive factor irrespective of the maternal age group in our study.

Anemia in pregnancy can subsequently cause a number of adverse outcomes, such as i) a small for gestational age and low birth weight baby, especially if the anemia is experienced in the first trimester[17], ii) preterm delivery, and iii) perinatal and neonatal mortalit[6, 18]. An anemic pregnant woman is less tolerable to peripartum bleeding than a non-anemic one, especially in patients at risk of postpartum hemorrhage. Anemic pregnant women are generally asymptomatic; thus, a healthy-looking, no underlying illness woman can still have the disease. The healthcare personnel responsible for the antenatal care should be cautious with pregnant women who are at risk, for example underweight or previously diagnosed with anemia, and should provide prompt treatment and monitor the patient's compliance in taking the proper amount of ferrous supplementation. If necessary, anemic patients who cannot tolerate oral iron supplementation/treatment may be provided with the parenteral form which has been proven to be more effective[19]. However, whether this anemia prevention method can improve perinatal outcomes is still unclear. Our limitation here was that our study did not originally plan to collect maternal and neonatal outcomes. Consequently, either a prospective or experimental study should be performed in the future to evaluate the effect of anemia and the efficacy of ferrous supplementation on the obstetrics and neonatal outcomes.

Determining the prevalence and rates of serological conversion concerning HIV and syphilis were also among the study objectives. HIV infection in pregnancy unfavorably affects both the mother and fetus. Early screening at the first prenatal visit and prompt treatment is advisable. Though, as mentioned elsewhere, it is still controversial to recommend repeated HIV screening in the third trimester. One study conducted in a high-prevalence area showed a 3% seroconversion rate[20]. We did not observe any cases of HIV seroconversion in our study population; nonetheless, concerns were raised considering the high prevalence observed (>1/1,000). The authors suggest a careful consideration to the RTCOG recommendation to repeat HIV serology in each institution's population during the third trimester.

Regarding syphilitic infection, the prevalence has been reported to broadly range between 0.7-400 per 100,000 pregnant population, as referenced by various reports worldwide, including one from Thailand[21-24]. It

is important to note that even in populations with an expected high prevalence of STIs, such as migrants and refugees, the prevalence of syphilis infection can be low[24]. Albright and colleagues reported that repeated syphilitic screening in the late trimester is not cost-effective in low prevalence populations[25]. Nevertheless, an increased incidence of congenital syphilis observed in a United States population between 2012 and 2014[26] demonstrated a contrary situation for considering implementing a stringent protocol for syphilis screening regardless of the background prevalence. The detection of seroconversion is notable because the only approach to prevent 98.2% of congenital syphilis is to provide treatment to the mother[27]. From our study, we anticipated a higher prevalence (1.8/1,000) and incidence of seroconversion than what was earlier expected (2 participants, incidence of 1.8/1,000). Moreover, both the seroconverting participants' history did not demonstrate much concern for STI infection (single partner, housewife, and no previous history of STI infection). As a result, the authors recommend repeated syphilitic serologic testing regardless of the STI risks. A cost-effectiveness study enrolling a larger population is also encouraged in the future.

## Conclusion

In conclusion, due to the dilution effect of the blood volume during pregnancy, a significant decrease in hemoglobin and hematocrit levels in the study warrants a repeated CBC test in the late trimester. Patients at a high risk of developing anemia in the second/third trimester included i) patients diagnosed with anemia at the first antenatal visit, ii) underweight patients, and iii) patients who have not complied with their ferrous supplementation/medication. These groups of patients require close monitoring to prevent or alleviate the severity of anemia during delivery. The authors also support repeated screening for syphilis owing to the present of syphilis seroconversion though further cost-effectiveness study should be performed in the future. Nonetheless, despite a considered high prevalence of HIV serology status, absent of HIV seroconversion warrants re-consideration of universal repeated screening of HIV infection in the third trimester. Each institution policy regarding the repeated antenatal blood tests should be based on diseases' prevalence and health setting.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## OBSTETRICS

# Prevalence of Gestational Diabetes Mellitus among Women with Lower Risk for Gestational Diabetes in Siriraj Hospital

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## ABSTRACT

**Objectives:** To determine prevalence of gestational diabetes (GDM) among Thai pregnant women who were at lower risk for GDM and determine possible associated factors.

**Materials and Methods:** A total of 292 pregnant women who had lower risk for GDM who started antenatal care before 20 weeks of gestation were included. All women received GDM screening and diagnosis with 50-g glucose challenge test and 100-g oral glucose tolerance test. Data were extracted from medical record, including baseline characteristics, obstetric data, GDM screening and diagnosis, and pregnancy outcomes. Prevalence of GDM was estimated. Various characteristics and pregnancy outcomes were compared between women with and without GDM. Logistic regression analysis was performed to determine independent risk factors associated with GDM adjusted for potential confounders.

**Results:** Mean age was 24.6 years and 59.2% were nulliparous. Mean body mass index (BMI) was 20.1 kg/m$^2$ and 22.9% were underweight. GDM was diagnosed in 36 women, corresponding to a prevalence of 12.3%. Of them, 8.2% were diagnosed before 24 weeks (early-onset) and 4.1% after 24 weeks (late-onset). Early-onset GDM contributed to 66.7% of GDM cases. GDM women had significantly higher age ($p = 0.041$) and BMI ($p = 0.016$) than those without GDM. Women who were > 25 - 29 years were significantly more likely to have GDM than those of ≤ 25 years (relative risk 1.91, 95% confidence interval 1.02-3.57, $p = 0.041$). The only independent associated factor associated with GDM was maternal age of > 25 - 29 years (adjusted odds ratio 2.21, 95% confidence interval 1.07-4.57, $p = 0.032$).

**Conclusion:** Prevalence of GDM among women with lower risk was 12.3%. Independent associated factor was maternal age of > 25 - 29 years.

**Keywords:** gestational diabetes, low risk, maternal age, risk factors, pregnancy outcomes.

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# *ความชุกของภาวะเบาหวานขณะตั้งครรภ์ในสตรีที่มีความเสี่ยงต่ำต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์*

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***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อศึกษาความชุกของภาวะเบาหวานขณะตั้งครรภ์ในสตรีที่มีความเสี่ยงต่ำต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์*

***วัสดุและวิธีการ:*** *ทำการศึกษาในสตรีที่มีความเสี่ยงต่ำต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์ที่มาฝากครรภ์ก่อนอายุครรภ์ 20 สัปดาห์ จำนวน 292 ราย สตรีตั้งครรภ์จะได้รับหารตรวจคัดกรองและวินิจฉัยภาวะเบาหวานขณะตั้งครรภ์ด้วยวิธี 50-g glucose challenge test และ 100-g oral glucose tolerance test ตามความเหมาะสม ทำการเก็บข้อมูลจากเวชระเบียน ได้แก่ ข้อมูลพื้นฐาน ข้อมูลทางสูติศาสตร์ ผลการตรวจคัดกรองและวินิจฉัยภาวะเบาหวานขณะตั้งครรภ์ และผลของการตั้งครรภ์ ทำการประเมินความชุกของภาวะเบาหวานขณะตั้งครรภ์ และทำการเปรียบเทียบข้อมูลต่างๆ ระหว่างสตรีตั้งครรภ์ที่มีและไม่มีภาวะเบาหวานขณะตั้งครรภ์ ทำการวิเคราะห์ด้วยวิธี logistic regression analysis เพื่อประเมินปัจจัยเสี่ยงต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์*

***ผลการศึกษา:*** *สตรีตั้งครรภ์มีอายุเฉลี่ย 24.6 ปี และร้อยละ 59.2 เป็นการคลอดครั้งแรก ค่าเฉลี่ยดัชนีมวลกายเท่ากับ 20.1 กก/ม$^2$ และร้อยละ 22.9 มีน้ำหนักต่ำกว่าเกณฑ์ พบภาวะเบาหวานขณะตั้งครรภ์ในสตรีตั้งครรภ์ 36 ราย คิดเป็นความชุกร้อยละ 12.3 ในสตรีตั้งครรภ์ดังกล่าว ร้อยละ 8.2 สามารถวินิจฉัยภาวะเบาหวานขณะตั้งครรภ์ได้ก่อนอายุครรภ์ 24 สัปดาห์ (early-onset) และร้อยละ 4.1 วินิจฉัยได้หลังอายุครรภ์ 24 สัปดาห์ (late-onset) กลุ่ม early-onset คิดเป็นร้อยละ 66.7 ของสตรีตั้งครรภ์ที่มีภาวะเบาหวานขณะตั้งครรภ์ทั้งหมด สตรีตั้งครรภ์ที่มีอายุ > 25 - 29 ปี มีภาวะเบาหวานขณะตั้งครรภ์สูงกว่ากลุ่มอายุ ≤ 25 ปี อย่างมีนัยสำคัญทางสถิติ (relative risk 1.91, 95% confidence interval 1.02-3.57, p = 0.041) ปัจจัยเสี่ยงที่สำคัญสำหรับการเกิดภาวะเบาหวานขณะตั้งครรภ์ได้แก่ อายุ > 25 - 29 ปี (adjusted odds ratio 2.21, 95% confidence interval 1.07-4.57, p = 0.032)*

***สรุป:*** *ความชุกของภาวะเบาหวานขณะตั้งครรภ์ในสตรีที่มีความเสี่ยงต่ำต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์เท่ากับร้อยละ 12.3 ปัจจัยเสี่ยงที่สำคัญสำหรับการเกิดภาวะเบาหวานขณะตั้งครรภ์ในสตรีที่มีความเสี่ยงต่ำต่อการเกิดภาวะเบาหวานขณะตั้งครรภ์ ได้แก่ อายุ > 25 - 29 ปี*

***คำสำคัญ:*** *ภาวะเบาหวานระหว่างตั้งครรภ์ ความเสี่ยงต่ำ อายุ ปัจจัยเสี่ยง ผลลัพธ์ของการตั้งครรภ์*

## Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical complications during pregnancy which can lead to various maternal and neonatal complications[1-4]. Prevalence of GDM has increased worldwide partly due to the epidemic of overweight and obesity[1-3]. Most international medical organizations recommend GDM screening for all pregnant women (universal screening) during 24-28 weeks of gestation but earlier screening might be considered among women at higher risk[1-4]. On the other hand, a selective, risk-based screening approach is used by some others[5-7]. Common risk factors for GDM include age of > 25 to > 35 years, overweight or obesity (body mass index (BMI) ≥ 25 kg/m$^2$), family history of DM, GDM or macrosomia in previous pregnancy[1, 5, 7, 8].

Previous studies reported that selective GDM screening among high-risk women could miss up to one-sixth of GDM cases. Among low-risk women, reported prevalence of GDM varied between studies from 2.4% to 14%, depending on study population, risk definition, and screening methods[5, 9, 10]. These women with undiagnosed GDM would receive inadequate treatment and could result in increased risk of GDM-related adverse pregnancy outcomes.

According to current guideline, a universal GDM screening is offered to all pregnant women attending antenatal care clinic at Siriraj Hospital, using a 2-step approach with 50-g glucose challenge test (GCT) and 100-g oral glucose tolerance test (OGTT). This results in overall GDM prevalence of approximately 20%. However, GDM prevalence in pregnant women with lower risk has not been evaluated systematically. The results could provide more understandings regarding the risk and associated factors of GDM among this group of women. This could also help further grading of GDM risks and improving screening strategy and care of these women in the future.

Therefore, the primary objective of this study was to determine prevalence of GDM among Thai pregnant women who had lower risk for GDM. In addition, possible associated risk factors for GDM in this group of women were evaluated and pregnancy outcomes were compared between women with and without GDM.

## Materials and Methods

A cross-sectional study was conducted after approval from Siriraj Institutional Review Board. A total of 292 singleton pregnant women who were at lower risk for GDM who started antenatal care before 20 weeks of gestation were included. In Siriraj Hospital, pregnant women were considered at high-risk for GDM if the women were ≥ 30 years, had family history of DM, had BMI ≥ 25 kg/m$^2$, had previous GDM, history of macrosomia, unexplained fetal death, or hypertension[11]. Sample size was calculated from estimated prevalence of GDM of 15%. At 95% significance level and 4.5% acceptable error, at least 267 women were required including 10% loss.

All women received GDM screening and diagnosis according to institutional guideline. A 50-g GCT was used as a screening test with 140 mg/dL cut-off value and a 100-g OGTT was used for GDM diagnosis using Carpenter and Coustan criteria. Screening was offered at first antenatal visit and repeated at 24-28 weeks of gestation if initial test results were normal[11]. Women diagnosed with GDM received nutritional counseling and advice on behavioral modification. Fasting and/or 2-hour postprandial plasma glucose were used for follow-up and evaluation of glycemic control with the cut-off levels of < 95 mg/dL and < 120 mg/dL, respectively. Insulin therapy was initiated when glycemic control was inadequate. Labor and delivery care were provided according to institutional guideline.

Data were extracted from medical records, including baseline characteristics, obstetric data, GDM screening and diagnosis, and pregnancy outcomes. Prevalence of GDM was estimated. Early-onset GDM was defined as GDM diagnosed before 24 weeks and late-onset GDM were those diagnosed at ≥ 24 weeks. Pre-pregnancy BMI was estimated from self-reported pre-pregnancy weight or weight before 14 weeks and measured height. BMI were categorized into underweight (< 18.5 kg/m$^2$) and normal weight (18.5 - 24.9 kg/m$^2$) according to Institute of Medicine recommendation. Gestational weight gain was also categorized according to Institute of Medicine (IOM) recommendation as well[12]. Newborn infants were classified by birth weight and gestational age into small for gestational age (SGA),

appropriate for gestational age (AGA), and large for gestational age (LGA), using cut-off at 10th and 90th percentile according to World Health Organization (WHO) birth weight percentile calculator, based on data from the same population[13].

Descriptive statistics were used to describe various characteristics, including mean, standard deviation, number, and percentages as appropriate. Student t test and chi square test were used to compare characteristics between women with and without GDM as appropriate. Relative risk (RR) and 95% confidence interval (CI) was estimated for assessing association between various characteristics and GDM. Logistic regression analysis was performed to determine independent risk factors associated with GDM adjusted for potential confounders and adjusted odds ratio (OR) was estimated. A p value of $< 0.05$ was considered statistically significant.

## Results

A total of 292 pregnant women who were at lower risk for GDM were included. Baseline characteristics of the women are shown in Table 1. Mean age was 24.6 years and almost 60% were nulliparous. Mean BMI was 20.1 kg/m$^2$ and 22.9% were underweight.

**Table 1.** Baseline characteristics of pregnant women (n = 292).

| Characteristics | |
|---|---|
| Mean age ± SD (years) | 24.6 ± 3.1 |
| Mean BMI ± SD (kg/m$^2$) | 20.1 ± 2.3 |
| Nulliparous | 173 (59.2) |
| BMI category | |
| Underweight | 67 (22.9%) |
| Normal weight | 225 (77.1%) |

SD: standard deviations, BMI: body mass index

All women received GDM screening and diagnosis according to institutional guideline and the results are shown in Table 2. Mean gestational age (GA) at first and second screening were 9.5 and 25.9 weeks, respectively. GDM was diagnosed in 36 women, corresponding to a prevalence of 12.3%. Of them, 8.2% were diagnosed before 24 weeks (early-onset) and 4.1% after 24 weeks (late-onset). Of early-onset GDM 50% were diagnosed in first trimester (4.1% of all women) and none of these cases had any sign or symptoms of long-term diabetic complications. Early-onset GDM contributed to 66.7% of GDM cases. Mean GA at diagnosis of early- and late-onset GDM were 10.8 and 27.7 weeks, respectively. All GDM cases had well-glycemic control by nutritional therapy that none required insulin therapy.

**Table 2.** GDM screening and diagnosis (n = 292).

| GDM screening and diagnosis | |
|---|---|
| Mean GA at first screening ± SD (weeks) | 9.5 ± 3.7 |
| Mean GA at second screening ± SD (weeks) | 25.9 ± 1.5 |
| GDM diagnosis | |
| No GDM | 256 (87.7%) |
| GDM | 36 (12.3%) |
| Early-onset GDM (GA < 24 weeks) | 24 (8.2%) |
| Late-onset GDM (GA ≥ 24 weeks) | 12 (4.1%) |
| Mean GA at second screening ± SD (weeks) | |
| Early-onset GDM (n = 24) | 10.8 ± 2.5 |
| Late-onset GDM (n = 12) | 27.7 ± 2.4 |

GDM: gestational diabetes mellitus, GA: gestational age, SD: standard deviations

Comparison of various characteristics were made between those with and without GDM and the results are presented in Table 3. GDM women had significantly higher age (p = 0.041) and BMI (p = 0.016) than those without GDM. Women who were > 25 - 29 years were significantly more likely to have GDM than those of ≤ 25 years (RR 1.91, 95%CI 1.02-3.57, p = 0.041). Women whose BMI were normal had higher risk of GDM than those who were underweight, but without statistical significance (RR 2.38, 95%CI 0.87-6.49, p = 0.071).

**Table 3.** Comparison of characteristic between pregnant women with and without GDM.

| Characteristics | No GDM n = 256 | GDM n = 36 | RR (95%CI) | p value |
|---|---|---|---|---|
| Mean age ± SD (years) | 24.4 ± 3.2 | 25.6 ± 2.4 | - | 0.043 |
| Mean BMI ± SD (kg/m$^2$) | 20.0 ± 2.3 | 21.0 ± 2.1 | - | 0.016 |
| Parity | | | | 0.333 |
| Nulliparous (n = 173) | 149 (86.1%) | 24 (13.9%) | 1.0 | |
| Multiparous (n = 119) | 107 (89.9%) | 12 (10.1%) | 0.73 (0.38-1.40) | |
| Age group | | | | 0.041 |
| ≤ 25 years (n = 160) | 146 (91.3%) | 14 (8.7%) | 1.0 | |
| > 25 - 29 years (n = 132) | 110 (83.3%) | 22 (16.7%) | 1.91 (1.02-3.57) | |
| BMI category | | | | 0.071 |
| Underweight (n = 67) | 63 (94.0%) | 4 (6.0%) | 1.0 | |
| Normal weight (n = 225) | 193 (85.8%) | 32 (14.2%) | 2.38 (0.87-6.49) | |

GDM: gestational diabetes mellitus, RR: relative risk, CI: confidence interval, SD: standard deviations, BMI: body mass index

Table 4 shows comparison of pregnancy outcomes between the 2 groups. GA at delivery was comparable and gestational weight gain was slightly lower among GDM women. Route of delivery was comparable between the 2 groups. Mean birth weight were comparable and rate of LGA was only slightly higher among GDM women. Other neonatal outcomes were comparable.

**Table 4.** Comparison of pregnancy outcomes for pregnant women with and without GDM.

| Characteristics | No GDM n = 256 | GDM n = 36 | p value |
|---|---|---|---|
| Mean GA at delivery ± SD (weeks) | 38.1 ± 1.4 | 38.4 ± 1.5 | 0.352 |
| Mean gestational weight gain ± SD (kg) | 15.4 ± 4.7 | 13.8 ± 4.6 | 0.060 |
| Gestational weight gain category | | | 0.091 |
| Normal | 93 (36.3%) | 13 (36.1%) | |
| Inadequate | 54 (21.1%) | 13 (36.1%) | |
| Excessive | 109 (42.6%) | 10 (27.8%) | |
| Route of delivery | | | 0.464 |
| Vagina delivery | 174 (68.0%) | 24 (66.7%) | |
| Primary cesarean section | 67 (26.2%) | 8 (22.2%) | |
| Repeat cesarean section | 15 (5.9%) | 4 (11.1%) | |
| Normal weight (n = 225) | 193 (85.8%) | 32 (14.2%) | |
| Preterm delivery | 21 (8.2%) | 2 (5.6%) | 0.581 |
| Preeclampsia | 9 (3.5%) | 0 (0%) | 0.253 |
| Mean birth weight ± SD (g) | 3,022.4 ± 425.2 | 3,086.9 ± 455.7 | 0.399 |
| Birth weight category | | | 0.843 |
| AGA | 205 (80.1%) | 28 (77.8%) | |
| SGA | 17 (6.6%) | 2 (5.6%) | |
| LGA | 34 (13.3%) | 6 (16.7%) | |

**Table 4.** Comparison of pregnancy outcomes for pregnant women with and without GDM. (Cont.)

| Characteristics | No GDM n = 256 | GDM n = 36 | p value |
|---|---|---|---|
| Asphyxia | 7 (2.7%) | 3 (8.3%) | 0.112 |
| Phototherapy | 35 (13.7%) | 4 (11.1%) | 0.799 |
| Neonatal hypoglycemia | 6 (2.3%) | 2 (5.6%) | 0.269 |
| NICU admission | 6 (2.3%) | 0 (0%) | 1.000 |

GDM: gestational diabetes mellitus, SD: standard deviations, AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, NICU: neonatal intensive care unit

Logistic regression analysis was performed to determine independent risk factor for GDM adjusted for potential confounders and the results are presented in Table 5. The only independent factor associated with GDM among these women was maternal age of > 25 - 29 years (adjusted OR 2.21, 95%CI 1.07-4.57, p = 0.032). Parity and BMI status were not significantly associated with GDM.

**Table 5.** Logistic regression analysis to determine independent risk factor for GDM adjusted for potential confounders.

| Risk factors | Adjusted OR (95%CI) | p value |
|---|---|---|
| Parity | | |
| Nulliparous | 1.0 | |
| Multiparous | 0.63 (0.30-1.33) | 0.225 |
| BMI | | |
| Underweight | 1.0 | |
| Normal weight | 2.57 (0.87-7.57) | 0.088 |
| Age group | | |
| ≤ 25 years | 1.0 | |
| > 25-29 years | 2.21 (1.07-4.57) | 0.032 |

GDM: gestational diabetes mellitus, OR: odds ratio, CI: confidence interval, BMI: body mass index

# Discussion

The result of this study showed that prevalence of GDM among pregnant women with lower risk for GDM was 12.3%. This was relative higher than what was reported from other studies[5, 10]. A nationwide study in Turkey reported GDM prevalence of 4.5% in low-risk women[10]. Another study in France reported GDM prevalence among women without any risk factor was as low as 2.4% that the authors suggested that screening tests could be avoided in low-risk women[5]. A study among low-risk pregnant women over 25 years in Malaysia showed GDM prevalence of 14%[9]. Differences in the reported prevalence might possibly due to differences in population characteristics and their baseline risk, definition of GDM risk factors, and screening strategies and approaches. The results of this study also showed that GDM was diagnosed at < 24 weeks in majority of cases. This was similar to a recent report from the same institution that early-onset GDM accounted for majority (65.9%) of all GDM[14].

From logistic regression analysis, women who were > 25 - 29 years were twice likely to have GDM compared to those ≤ 25 years (adjusted OR 2.21). Similar to other previous studies, increasing age has been related to the increase in GDM[10, 15, 16]. A recent systematic review reported that GDM risk exhibited a linear relationship with maternal age (increase by 12.74% for each year)[17]. Another recent study in China also reported that the risk of GDM increased by an average of 8% for every 1 year of maternal age[18]. Pre-pregnancy BMI has been consistently associated with GDM, especially overweight and obesity[1-4, 8, 10, 16, 19].

However, in this study, having normal BMI did not significantly increase the risk of GDM compared to those who were underweight.

Pregnancy outcomes were comparable between women with and without GDM. Gestational weight gain among GDM women tend to be lower and less likely to have excessive weight gain. This was similar to other reports from the same institution[14, 20]. Lower weight gain in GDM women could possibly due to intensive counseling and monitoring, as well as increased awareness of the women themselves. Rate of LGA was only slightly higher in GDM women without statistical significance. However, the rate was lower than those previously reported among GDM with at least 1 risk factor of more than 20%[14, 20]. The results were similar to previous report that these GDM among low-risk women seemed to be milder and less likely to have perinatal complications[5]. However, if these women with lower risk were not screened and GDM was missed, adverse pregnancy outcomes could increase from not receiving adequate treatment. Even GDM cases among low-risk women were milder, benefits of treatment of mild GDM have been established and pregnancy outcomes could improve[21].

Some limitations should be addressed. Sample size might be limited for subgroup analysis and some outcomes were infrequent that preclude further detailed analysis. Only clinical and personal risk factors were evaluated. Effects of treatment provided on pregnancy outcomes could not be measured. Further, larger studies are still needed to elucidate the importance of GDM screening in women with lower risk. Other biological, genetic, and other possible risk factors should be further evaluated and measures to improve pregnancy outcomes should be investigated. The results can also be used as a baseline information for future development of risk scoring system for women with different risk profiles.

Taken together, current approach of universal screening started early in pregnancy is seem to be reasonable and should be continued. As being Asian has been reported to be a high-risk population[1, 2]. Thai women could also considered as such and every woman should receive appropriate GDM screening. Universal screening can detect considerable proportion of GDM in women with lower risk and, of them, two-thirds of cases could be diagnosed early in pregnancy. Although GDM cases seem to be milder and adverse pregnancy outcomes did not differ significantly from those without GDM, early identification and treatment could help minimize related adverse outcomes of these women.

## Conclusion

In conclusion, prevalence of GDM among women with lower risk for GDM was 12.3%. The only independent factor associated with GDM among low-risk women was maternal age of > 25 - 29 years. Pregnancy outcomes were comparable between those with and without GDM.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

# Reliability of the Cervamet and POPstix in Pelvic Organ Prolapse Quantification Measurement

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## ABSTRACT

**Objectives:** The primary objective was to evaluate the reliability of Cervamet and POPstix in pelvic organ prolapse quantification (POP-Q) measurement by 2 different groups of experienced physicians. The secondary objectives were to study time used for examination and patients' discomfort scores.

**Materials and Methods:** 156 Thai pelvic organ prolapse women attending a gynecology clinic at King Chulalongkorn Memorial Hospital from October 2019 to July 2020 participated in the study. The participants who underwent POP-Q measurement were divided into 4 groups: group1: two staffs using Cervamet, group 2: two staffs using POPstix, group 3: two residents using Cervamet, and group 4: two residents using POPstix. The results were blinded to one another. The time used for examination and the patients' discomfort score were recorded.

**Results:** The reliabilities (intraclass correlation coefficient) were good in both resident groups: POPstix (0.75-0.98) and Cervamet (0.76-0.98) and in the staffs group: POPstix (0.75-0.95) and Cervamet (0.78-0.96). The median of the time used by the resident group was higher than in the staff group (POPstix: 1.71 vs 1.45 minutes, Cervamet: 3.04 vs 1.99 minutes) ($p < 0.01$). There was no statistical difference in the patients' discomfort scores in all groups.

**Conclusion:** The Cervamet was a non-disposable tool which equivalent reliability when compared to the POPstix that could be considered as an alternative for POP-Q measurement.

**Keywords:** pelvic organ prolapse, POP-Q, POPstix, cervamet, reliability.

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# *การศึกษาความเที่ยงในการประเมินภาวะอุ้งเชิงกรานหย่อนด้วยเครื่องมือ Cervamet and POPstix*

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***บทคัดย่อ***

***วัตถุประสงค์:*** *วัตถุประสงค์หลักเพื่อศึกษาความเที่ยงของเครื่องมือ Cervamet และ POPstix ในการประเมินตำแหน่ง และระดับความรุนแรงของอวัยวะอุ้งเชิงกรานหย่อนด้วยวิธี pelvic organ prolapse quantification (POP-Q) ระหว่างกลุ่มแพทย์ที่มีประสบการณ์ต่างกันสองกลุ่มในการตรวจ POP-Q วัตถุประสงค์รองเพื่อศึกษาเวลาที่ใช้ตรวจ และความไม่สบายตัวในการตรวจ POP-Q โดยเครื่องมือทั้ง 2 ชนิด*

***วัสดุและวิธีการ:*** *ผู้หญิงภาวะอุ้งเชิงกรานหย่อน จำนวน 156 คน ที่มารับบริการตรวจในคลินิกนรีเวชกรรม ณ โรงพยาบาลจุฬาลงกรณ์ ในช่วงเดือน ตุลาคม 2562 – กรกฎาคม 2563 จะถูกแบ่งออกเป็น 4 กลุ่ม [กลุ่ม 1 = อาจารย์แพทย์ 2 คน ใช้เครื่องมือ Cervamet, กลุ่ม 2 = แพทย์ประจำบ้าน 2 คน ใช้เครื่องมือ POPSTIX, กลุ่ม 3 = อาจารย์แพทย์ 2 คน ใช้เครื่องมือ POPstix, และ กลุ่ม 4 = แพทย์ประจำบ้าน 2 คน ใช้เครื่องมือ POPSTIX] โดยที่ผู้ตรวจจะไม่ทราบผลการตรวจของอีกคน โดยมีการบันทึกเวลาที่ใช้ตรวจ และให้ผู้ป่วยประเมินคะแนนความไม่สบายตัว*

***ผลการศึกษา:*** *ค่าสัมประสิทธิ์สหสัมพันธ์ภายในของเครื่องมืออยู่ในเกณฑ์ดี ทั้งในกลุ่มแพทย์ประจำบ้าน: POPstix (0.75-0.98), Cervamet (0.76-0.98) และในกลุ่มอาจารย์แพทย์ : POPstix (0.75-0.95), Cervamet (0.78-0.96) ค่ามัธยฐานของระยะเวลาที่ใช้ในแพทย์ประจำบ้านมากกว่าในกลุ่มอาจารย์แพทย์ (POPstix: 1.71 vs 1.45 นาที, CERVAMET: 3.04 vs 1.99 นาที ) อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) คะแนนความไม่สบายตัวของ 4 กลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ*

***สรุป:*** *เครื่องมือ Cervamet เป็นอุปกรณ์ที่สามารถนำมาใช้ซ้ำได้ และมีความเที่ยงเช่นเท่ากับ POPstix จึงเหมาะสมที่จะเป็นอีกหนึ่งทางเลือกที่จะนำมาใช้ในการประเมินตำแหน่ง และระดับความรุนแรงของอวัยวะอุ้งเชิงกรานหย่อนด้วยวิธี POP-Q*

***คำสำคัญ:*** *ภาวะอุ้งเชิงกรานหย่อน, POP-Q, POPstix, Cervamet, ความเที่ยง*

## Introduction

Pelvic organ prolapse quantification (POP-Q) system is an assessment of pelvic organ descent. It has been accepted by the American College of Obstetricians and Gynecologists (ACOG), the International Continent Society (ICS), the American Uro-gynecologic Society (AUGS), and the Society of Gynecologic Surgeons (SGS) as a standard protocol for classification and staging of the disease which is used for the communication between physicians and for research purpose[1]. POP-Q examination contains the 6 anatomical points; Aa = length of anterior vaginal wall 3 cm proximal to external urethral meatus, Ba = length of most distal/dependent part of any portion of anterior vaginal wall just anterior to vaginal cuff/anterior lip of cervix, C = length of most distal edge of cervix, Ap = length of posterior wall 3 cm proximal to hymen, Bp = length of most distal/dependent part on posterior vaginal wall, D = length of posterior fornix or pouch of Douglas which are measured in centimeters by using the hymen lining as a reference point and 3 anatomical markers; genital hiatus (GH), perineal body (PB), total vaginal length (TVL). The leading points that are superior to the hymen will be recorded as the negative numbers. The point below the hymen will be recorded as the positive numbers. The 6 anatomical points were grouped in 3 compartments: anterior, middle, and posterior. Then each compartment was classified as the stage 1-4 according to the distance of prolapse from hymen[2]. These 6 anatomical points and 3 anatomical landmarks are used for staging and for follow-up after treatments. There was a report of good interobserver and intraobsever reliability for POP-Q measurement (intraclass correlation 0.7 - 0.9) using the ring forceps and the instrument for POP-Q measurement[3].

There had been several different instruments introduced for POP-Q measurement such as the fingers, ring forceps, spatula, cotton swabs, etc. but there were differences in the methodology design and parameter used for outcome measurement[3, 4]. In a comparative study of using spatula versus POPstix in POP-Q measurement, POP-Q points using POPstix had a good to excellent reliability except for PB and TVL. The interobserver reliability and the agreement for the staging of POP-Q were better in the POPstix group than in the spatula group[5]. The authors suggested using POPstix device to improve the accuracy of POP-Q measurement[5]. Another study in 2016, comparative study of using digital assessment and quantification of pelvic organ prolapse (DPOP-Q) versus POPstix® in POP-Q measurement, result shown DPOP-Q had high interobserver and intraobserver reliability and significant quicker and less uncomfortable than POPstix®[6]. The International Urogynecological Association (IUGA) has recommended choosing the POPstix as the standard instrument for POP-Q measurement; however, this was not widely adopted because of its relatively high cost and non-reusable materialization. Hence, the reusable equipment can be rather helpful in lowering the long-term cost in POP-Q measurement.

The research team from the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University and the Prosthetic and Orthopedic Implant center, Mechanical Engineering Department, Faculty of Engineering, Chulalongkorn University have developed the Cervamet, a new device to be used in POP-Q evaluation. This instrument is designed as a rod shape with measurement in centimeters and millimeters (ruler-like scale), and with the sliding sleeve bar. This instrument which is made from aluminum, has very light weight, and it can be reused many times. Therefore, in order to implement this new measuring reusable equipment, the psychometric study (reliability) should be conducted and published.

The primary objective of this study was to evaluate the interrater reliability of Cervamet and POPstix in POP-Q measurement. The secondary objectives were to evaluate time used to perform the POP-Q examination and the patients' discomfort between the Cervamet and POPstix.

## Materials and Methods

This cross-sectional study was carried out at the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok,

Thailand from October 2019 to July 2020. The research protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. Thai women with pelvic organ prolapse stage 1-4 participated in the study. Inclusion criteria were women aged 35 - 65 years and with body mass index (BMI) 18.5 - 30 kg/m$^2$. Exclusion criteria were pregnancy, pelvic mass, and history of pelvic surgery.

The women were randomly divided by using the block of four technique into 4 groups (Fig. 1), based on examiners and instrument types. Each patient was examined by two physicians consecutively and only one instrument to prevent discomfort from examination; group 1: two staffs using Cervamet and, group 2: two staffs using POPstix, group 3: two residents using Cervamet, and group 4: two residents using POPstix. (Fig. 2) Standardization of the POP-Q measurement technique for all examiners were done before beginning the study follow by Bump et al[7]. The patients were examined in lithotomy position for POP-Q measurement while straining. The POP-Q points were measured by using the POPstix by the standard technique described by Bump et al[7]. The POP-Q anatomical points measured by Cervamet were done by placing the tip of Cervamet (Fig. 3) at each different POP-Q points, then the sliding knob was moved to the hymen level. Switching of the location of the tip of Cervamet and the sliding knob was required in case of anatomical POP-Q point protruding beyond the hymen. The distance from POP-Q point to the hymen was displayed on the scale at lower part of measurement rod (in millimeters).

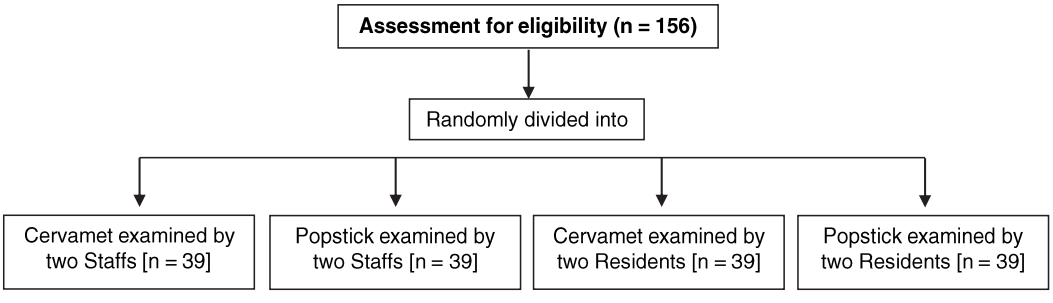


**Fig. 1.** Flow diagram.


**Fig. 2.** POPstix.

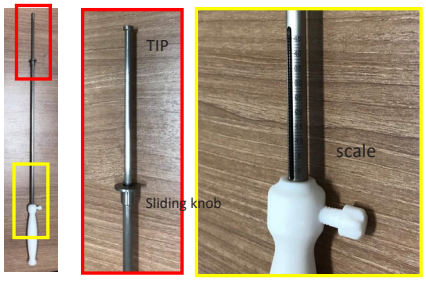


**Fig. 3.** Cervamet.

Patients' demographic data, such as age, weight, height, menopause status, and the numbers of children, were recorded. The time used by each examiner and the patients' discomfort score (Likert scale 1-5; 1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe, 5 = worst) were recorded by the nurse assistant and such results were blinded to other examiner.

The sample size for the reliability test study was estimated according to the formula for sample size and optimal designs for reliability studies[8]. We used the intraclass correlation coefficient (ICC) of the TVL (POP-Q anatomical distance) with the ICC of 0.8 from our pilot study. From our pilot study (n = 10), the PB had the lowest ICC that was expected for the highest sample sizes. The p1 was 0.8, p0 (minimally acceptable level of reliability) was 0.6, $\alpha$ was 0.05, and $\beta$ was 0.2. The value of p0 was estimated from acceptable error (20%) of p1 (0.8×0.5 = 0.16 - 0.2). The sample size estimation was 39 cases per group. The total sample was 156 cases.

Statistical analysis was carried out by SPSS software version 22.0. Categorical variables were presented as frequency and percentages, whereas continuous variables were presented as mean and standard deviation. ICC was used to calculate the reliability of Cervamet and POPstix in POP-Q measurement. Student's t test was used for comparison of the discomfort scores and duration of examinations. A p value < 0.05 was considered statistically significant.

## Results

One hundred and fifty-six patients participated in this study (39 patients in each group) as shown in Fig. 1. The demographic data of the study population are presented in Table 1. Most patients were aged between 50 to 60 years old (Table 1). The ICC values in the resident group are shown in Table 2. Values were similar in both Cervamet and POPstix (in the range of 0.75-0.98 and 0.76-0.98, respectively). The lowest value of ICC for each instrument were 0.75 (PB) in POPstix and 0.76 (TVL) in Cervamet, respectively.

**Table 1.** Patients' characteristics (n = 156).

| Variable | Total |
|---|---|
| Age (years) | 58.23 ± 7.98 |
| Weight (kg) | 58.67 ± 8.66 |
| Height (cm) | 154.27 ± 6.70 |
| Body mass index (kg/m$^2$) | 24.60 ± 3.20 |
| Menopause (years) | 49.85 ± 4.02 |
| Number of Child | |
| Nulliparous | 15 (9.6) |
| 1 child | 28 (17.9) |
| 2 children | 52 (33.3) |
| 3 children | 35 (22.5) |
| > 3 children | 26 (16.7) |
| POP stage | |
| Stage 1 | 43 (27.6) |
| Stage 2 | 50 (32.0) |
| Stage 3 | 38 (24.4) |
| Stage 4 | 25 (16.0) |
| Constipation | 18 (11.5) |
| Lifting heavy object | 17 (10.9) |

Data are presented as mean ± standard deviation and n (%), POP: pelvic organ prolapse

**Table 2.** Patients' characteristics (n = 156).

| | POPstix | Cervamet |
|---|---|---|
| POP-Q point, Intraclass correlation coefficient (95% confidence interval) | | |
| Aa | 0.98 (0.97, 0.99) | 0.98 (0.97, 0.99) |
| Ba | 0.96 (0.93, 0.98) | 0.95 (0.92, 0.98) |
| Ap | 0.84 (0.72, 0.91) | 0.89 (0.81, 0.94) |
| Bp | 0.77 (0.61, 0.87) | 0.94 (0.90, 0.97) |
| C | 0.97 (0.95, 0.98) | 0.94 (0.89, 0.97) |
| D | 0.95 (0.91, 0.97) | 0.94 (0.89, 0.97) |
| TVL | 0.83 (0.70, 0.91) | 0.76 (0.58, 0.86) |
| GH | 0.85 (0.73, 0.92) | 0.83 (0.70, 0.91) |
| PB | 0.75 (0.58, 0.86) | 0.88 (0.79, 0.94) |

POP-Q: pelvic organ prolapse quantification

ICC values in the staff group are displayed in Table 3. Values were also similar in both Cervamet and POPstix (in the range of 0.75-0.94 and 0.78-0.96 respectively). The lowest value of ICC shown 0.75 (TVL) in POPstix and 0.78 (PB) in Cervamet.

**Table 3.** Intraclass correlation coefficient in staff group.

| | POPstix | Cervamet |
|---|---|---|
| POP-Q point, Intraclass correlation coefficient (95% confidence interval) | | |
| Aa | 0.94 (0.89, 0.97) | 0.95 (0.92, 0.98) |
| Ba | 0.91 (0.83, 0.95) | 0.96 (0.92, 0.98) |
| Ap | 0.92 (0.86, 0.96) | 0.84 (0.72, 0.91) |
| Bp | 0.90 (0.82, 0.95) | 0.88 (0.78, 0.93) |
| C | 0.90 (0.82, 0.95) | 0.88 (0.78, 0.94) |
| D | 0.95 (0.90, 0.97) | 0.96 (0.92, 0.98) |
| TVL | 0.75 (0.56, 0.86) | 0.79 (0.63, 0.88) |
| GH | 0.79 (0.64, 0.89) | 0.79 (0.64, 0.89) |
| PB | 0.76 (0.59, 0.87) | 0.78 (0.63, 0.88) |

POP-Q: pelvic organ prolapse quantification

In the resident group, the median time (interquartile range (IQR)) spent in POP-Q measurement using POPstix was significantly shorter than the time spent using Cervamet [1.71 (1.52, 2.30) vs 3.04 (2.84, 3.27) minutes, $p < 0.001$] (Table 4). In the staff group, the median time for POPstix was 1.45 (1.23, 1.70) minutes, which was also significantly lower than the time for Cervamet [1.99 (1.75, 2.37) minutes] (Table 4).

**Table 4.** Time (minutes) uses for POP-Q measurement.

| | POPstix | Cervamet | p value (a) |
|---|---|---|---|
| Residents | 1.71 (1.52, 2.30) | 3.04 (2.84, 3.27) | < 0.001 |
| Staffs | 1.45 (1.23, 1.70) | 1.99 (1.75, 2.37) | < 0.001 |
| p value (b) | < 0.001 | < 0.001 | |

Data are presented as median (interquartile range), Data were analyzed with Mann-Whitney U test (a) compare between instrument, (b) compare between physicians' group, POP-Q: pelvic organ prolapse quantification

Comparing between the staff group and resident group, the timed used for POPstix and Cervamet were significantly lower in the staff group (1.45 vs 1.71 min, 1.99 vs 3.04 min). The discomfort scores of all study groups were cross compared as shown in Table 5.

**Table 5.** Discomfort scores in POP-Q measurement.

| | POPstix | Cervamet | p value (a) |
|---|---|---|---|
| Residents group | 1 (1, 2) | 2 (1, 2) | 0.667 |
| Staffs group | 2 (1, 3) | 2 (1, 2) | 0.344 |
| p value (b) | 0.212 | 0.952 | |

Data are presented by median (interquartile range)
Data were analyzed with Mann-Whitney U test (a) compare between instrument, (b) compare between physician hierarchy
Note: score 1 = lowest discomfort, 5 = highest discomfort
POP-Q: pelvic organ prolapse quantification

# Discussion

From our study, the POPstix and Cervamet yielded good to excellent reliability in both resident group and staff group, according to the classification by Koo and Li[9]. The ICC in both groups were more than 0.75 which resulted in good to excellent reliability. We found the good to excellent reliability in all POP-Q measurement points. The time used in POP-Q measurement depends on the experience. The resident spent more time for both equipments than the staff. In both staff group and resident group, the Cervamet required more time when compared to POPstix. We found difference in the discomfort scores of patients after the measurement by POPstix and Cervamet.

The good to excellent reliability of POPstix in our study was similar to the previous study by Hayward et al[5]. They also reported similar lowest reliability of the point of PB and TVL as in this study. This can be explained by the curve surface of the perineum (for PB) and different force to stretch the vagina when measuring the TVL. We found that the Cervamet had excellent reliability similar to POPstix in both staff group and resident group in overall point of POP-Q. We also found that Cervamet needed more time for measuring than the POPstix, but there was no difference in patients' discomfort scores. The Cervamet can be cleaned and is reusable. It is also ecofriendly (while POPstix is made of wood and cannot be reused). Although Cervamet is a time-consuming instrument in POP-Q measurement, it is reusable and having comparable reliability when compared to the internationally recommended POPstix. Moreover, it is ecofriendly and can help lowering the long-term cost of utilizing disposable materials. Therefore, we advocate choosing Cervamet as a reusable option for POP-Q measurement for clinical and research purpose.

### *The strengths in this study*

Our study included the two different experienced groups of examiners (residents, staffs) in order to confirm the reliability in different experienced operators. The Cervamet is the new tool, developed by the engineering staffs that are specialized in medical equipment development from Chulalongkorn University. This instrument prototype was finalized after the design corrections, and it was tested in the models before its application in the human for safety purpose.

### *The limitation of this study*

There was no comparison of the accuracy of POP-Q measurement using Cervamet and POPstix in the same patient due to ethical consideration. The IRB for this study only allowed for one equipment for one patient by two doctors.

# Conclusions

With equivalent reliability when compared to the internationally recommended POPstix, the Cervamet

could be considered as an alternative, non-disposable tool for POP-Q measurement.


## Acknowledgement

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

# The Effect of Simethicone on the Length of Hospital Stay of Patients Undergoing Laparotomy for Benign Gynecological Procedures with an Enhanced Recovery after Surgery Protocol: A randomized controlled trial

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## ABSTRACT

**Objectives:** To evaluate the efficacy of simethicone in treating postoperative ileus symptoms assessed by length of hospital stay, for patients undergoing elective laparotomy for benign gynecological procedures in the setting of an enhanced recovery after surgery (ERAS) protocol and to identify factors associated with a decreased length of hospital stay.

**Materials and Methods:** A single-center randomized controlled trial (TCTR20210204012) was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between February and June 2021. In all, 182 patients were randomized into 2 groups: an "immediate-simethicone-administration-group" (administered 160 mg of simethicone immediately after surgery; n = 91) and a "non-immediate-simethicone-administration-group" (no immediate simethicone used; n = 91). The lengths of stay and other hospital data were analyzed.

**Results:** No significant difference was observed in the lengths of stay of the immediate-simethicone-administration and non-immediate-simethicone-administration groups (p = 0.132), nor in their incidences of postoperative nausea/vomiting, abdominal discomfort, and diarrhea. A multivariate analysis found that the significant predictor of a decreased length of hospital stay was an estimated blood loss of < 500 mL (odds ratio 5.82, 95% confidence interval 1.20, 28.16, p = 0.029).

**Conclusion:** Immediately chewing simethicone after surgery had no effect on the length of hospital stay in cases of benign laparotomy for gynecological procedures in the setting of an ERAS protocol. An estimated blood loss below 500 mL was a predictor of early hospital discharge.

**Keywords:** ERAS, length of hospital stay, simethicone, benign surgery, laparotomy.

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# *การศึกษาผลของยาไซเมทิโคนต่อจำนวนวันในการนอนโรงพยาบาล ในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็ง ตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol), การทดลองแบบสุ่มและมีกลุ่มควบคุม*

***กานต์ชนก แตมามุ, สุชาดา อินทวิวัฒน์***

***บทคัดย่อ***

***วัตถุประสงค์:*** *ศึกษาผลของยาไซเมทิโคนในการรักษาภาวะลำไส้หยุดทำงานหลังผ่าตัด ที่มีผลต่อจำนวนวันในการนอนโรงพยาบาล ในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็งตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) และเพื่อศึกษาปัจจัยที่ช่วยลดจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัด*

***วัสดุและวิธีการ:*** *การวิจัยจัดทำขึ้นที่ภาควิชาสูติศาสตร์นรีเวชวิทยา คณะแพทยศาสตร์ ศิริราชพยาบาล มหาวิทยาลัยมหิดล, ประเทศไทย ระหว่างเดือนกุมภาพันธ์ถึงมิถุนายน พ.ศ.2564 โดยผู้ป่วยทั้งหมด 182 คน ถูกแบ่งเป็น 2 กลุ่ม คือกลุ่มที่ได้รับยาไซเมทิโคนหลังผ่าตัดทันที (91 คน) และกลุ่มที่ได้รับยาไซเมทิโคนทีหลัง (91 คน) โดยเก็บข้อมูลจำนวนวันที่นอนโรงพยาบาลหลังผ่าตัดและข้อมูลอื่นๆ ระหว่างนอนโรงพยาบาล*

***ผลการศึกษา:*** *จำนวนวันในการนอนโรงพยาบาลหลังผ่าตัดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มที่ได้รับยาไซเมทิโคนหลังผ่าตัดทันที และ กลุ่มที่ได้รับยาไซเมทิโคนทีหลัง ($p = 0.132$) อีกทั้งความชุกในการเกิดอาการคลื่นไส้อาเจียน, ท้องอืด, และท้องเสียก็ไม่มีความแตกต่างกันระหว่าง 2 กลุ่ม แต่จากการวิจัยพบว่าอัตราการเสียเลือดในห้องผ่าตัดที่น้อยกว่า 500 มิลลิลิตร เป็นตัวแปรสำคัญที่ลดจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัด (OR 5.82 [1.20, 28.16]; $p = 0.029$).*

***สรุป:*** *การได้รับยาไซเมทิโคนเคี่ยวทันทีหลังผ่าตัดไม่มีผลต่อจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัดในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็งตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) แต่อัตราการเสียเลือดในห้องผ่าตัดที่น้อยกว่า 500 มิลลิลิตร เป็นตัวแปรที่บ่งชี้การกลับบ้านได้เร็วขึ้นหลังผ่าตัด*

***คำสำคัญ:*** *ERAS, ระยะเวลาพักรักษาตัวในโรงพยาบาล, ไซเมทิโคน, การฟื้นตัวหลังผ่าตัด, การผ่าตัดส่องกล้อง*

## Introduction

Enhanced recovery after surgery (ERAS) protocols are multimodal, perioperative care pathways. The overriding aim of ERAS protocols is to improve postoperative recovery of patients undergoing major surgery. The concept of enhanced recovery programs was formulated by Professor Henrik Kehlet in the 1990s as part of European collaboration on colorectal surgery. The use of ERAS protocols for laparotomies and laparoscopies has since been widely studied, and they have proven to be safe for colorectal, vascular, and urological surgeries. The protocols were associated with comparable postoperative complications, shorter hospital stays, and reduced readmissions rates[1]. In an earlier study of gynecological surgery, the length of stay was significantly reduced after introducing ERAS protocols, declining from a mean of 2.6 days to 2.3 days, with no difference in complication, re-operation, or re-admission rates[2].

The ERAS pathways are comprised of many elements. They are preoperative counseling; preoperative bowel preparation; a venous thromboembolism prophylaxis; surgical-site infection reduction; standardized analgesic and anesthetic regimens; perioperative fluid management; perioperative nutrition; early mobilization; prevention of postoperative ileus; the avoidance of prolonged preoperative fasting, a large infusion volume, and extended Foley catheter usage; and a discharge pathway.

Postoperative ileus is an outcome of major abdominal surgery. The condition not only contributes to significant morbidity, but also prolongs length of hospital stay and increases treatment costs. The characteristics of ileus include reduced motility and intestinal dysfunction, resulting in an ineffective transit of intestinal contents. Postoperative ileus has a multifactorial pathogenesis that is only partially understood. It has been hypothesized that the pathogenesis is related to physical manipulation of the bowel; complex interactions between surgical stress and inflammatory mediators; the use of anesthetics; the analgesic methods employed; and perioperative fluid and electrolyte imbalances[3]. The reported incidence rate of postoperative ileus has differed between studies and surgical specialties; in the case of major abdominal surgery, it ranged between 10% and 30%[3] and affected about 14% of patients after laparotomies for gynecological procedures[4]. To date, there are few pharmacological interventions that shorten the duration of postoperative ileus. This is despite numerous studies having evaluated a range of pharmacological strategies to reduce ileus. The aims of those medications were to target the pathophysiology of ileus by minimizing sympathetic inhibition of gastrointestinal motility, inhibiting acetylcholinesterase activity, stimulating enteric motility, or decreasing inflammatory cascades[5]. For instance, numerous studies have investigated the chewing of gum. It is thought to stimulate the cephalon-vagal pathway, resulting in increased salivary and pancreatic secretions and an attendant improvement in gut motility[9]. The systematic and meta-analyses have found that the chewing of gum only minimally improves recovery from postoperative ileus[7, 10]. Nevertheless, the tested medications are not routinely used as they have not yet been adequately studied or they have not shown therapeutic efficacy.

Alternative agents (such as laxatives or antiflatulent drugs) are generally considered low-risk interventions to prevent ileus. One of these is simethicone. Simethicone is an activated dimethicone. Its large polymer consists of silicone, to which has been added silicon dioxide to increase the defoaming effects of simethicone. The drug is an inexpensive, readily available, and orally administered antifoaming agent comprised of polydimethylsiloxane and hydrated silica gel. It causes intestinal tract gas bubbles to coalesce, thereby facilitating their emission and preventing gas from forming at intestinal wall[6]. Simethicone coats the gastrointestinal tract and thus protects it from the harmful effects of gastric acid, acetylsalicylic acid, and biliary salts. In terms of its pharmacokinetics, simethicone is not absorbed by

the gastrointestinal tract; in addition, it does not disturb gastric acid secretion or mineral absorption. The drug is excreted in its original form in feces. The side effects of simethicone are nausea, vomiting, diarrhea, and headache, but they have been reported by only 2% - 5% of patients[6].

Few randomized controlled trials have evaluated the effects of simethicone on ileus, in terms of its impact on the length of hospital stay, following benign laparotomies for gynecological procedures in the setting of an ERAS protocol. The current investigation assessed simethicone's impact on the length of stay of Thai patients undergoing laparotomies for benign gynecological procedures with an ERAS protocol and also identified factors associated with a decreased length of hospital stay.

## Materials and Methods

This single-center, randomized controlled trial compared the use and non-use of immediately simethicone in patients undergoing laparotomies for benign gynecological procedures with an ERAS protocol. The investigation was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between February and June 2021. The trial was registered at the Thai Clinical Trials Registry (TCTR20210204012). Before commencement of the research, its protocol was approved by the Siriraj Institutional Review Board (Si 089/2020). Written informed consent was obtained from all participants. Patients were enrolled if they were aged over 18 years and met neither of the exclusion criteria (a documented allergy to simethicone, or undergoing emergency surgery). The participants were consecutively recruited at the time of appointment for blood results before surgery at the outpatient unit and repeatedly on the day before surgery. However, patients were withdrawn if they were subsequently found to have injury to the bowel mucosa or a pathology report of cancer, or if they were admitted postoperatively to the intensive care unit.

The data that were collected were the characteristics of the patients and details of their operative procedures and hospitalization. The patient characteristics comprised age, body mass index, menopausal status, blood pressure, and heart rate. The operative data were collected from each participant's medical records. They consisted of the operation type, operating time, anesthetic method, type of incision, estimated blood loss, and postoperative diagnosis. During the participants' hospital stay, the research staff visited the patients between 7-8 AM daily. The staff assessed the following: abdominal distension, bowel movements, passage of flatus, and gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea, and abdominal discomfort). In addition, the medical charts were reviewed to collect daily data on the patients' usage of simethicone and antiemetics, the presence of nausea/vomiting, the frequency of postoperative ileus, and average pain scores. The length of stay was also eventually recorded. In accordance with the ERAS protocol, its period was based on a discharge date that was determined by the clinical status of each patient, rather than a date desired by a patient. The discharge criteria are ability to tolerate regular diet without nausea or vomiting, oral anesthesia, and full mobilization.

### *Treatment allocation and trial medications*

Using block of 2 randomization, a random number generator was employed to assign patient numbers for the experimental (simethicone) and non-drug regimen (non-simethicone) groups. A research assistant (a nurse) enclosed and sealed the computer-generated numbers, which were written on cards, in opaque envelopes. The nurse later opened the envelopes and dispensed the trial drugs to participants in accordance with the numbers.

After giving their consent to take part in the study, participants were randomized into either the immediately used simethicone or non- immediately used simethicone study arm. The patients randomized to the immediately used simethicone group were instructed to chew 2 simethicone tablets (80 mg in

total) immediately after their arrival at the postoperative floor. However, the participants in the non- immediately used simethicone group were not given this medicine. Although the participants and the research staff were not masked to the group assignments, the surgeons were.

### *Siriraj ERAS protocol*

We followed the standardized Siriraj ERAS protocol for all patients. It involves fasting time, the mean tine of fasting is 10 hours which was reduced from the previous practice in Siriraj hospital. The mechanical bowel preparation with unison enema was performed in almost all elective patients, except some cases with difficult operation, Swiff solution was used instead. The administering of an intravenous antibiotic as a prophylaxis 1 hour before the skin incision. Typically, the antibiotic used was cephalosporins or ampicillin; if a patient was allergic to those drugs, clindamycin was given instead. The skin was cleaned with a chlorhexidine solution, with swabbing of the vagina prior to the insertion of a catheter and draping of the abdomen. Multimodal analgesia (such as patient-controlled epidural anesthesia combined with intravenous anesthesia) was utilized intraoperatively for some patients because of its ability to produce analgesic synergism and reduce adverse effects.

Early postoperative feeding with fluids commenced immediately upon regain of consciousness on the day after surgery. Feeding was later upgraded to a soft diet on the first day, and it was soon followed by a regular diet. However, if severe intraoperative abdominal adhesions, significant nausea and vomiting, or abdominal distension developed, oral feeding was withheld. It was restarted soon after resolution of the symptoms. An antifoaming agent and an iso-osmotic laxative were given if any gastrointestinal symptoms appeared. The fluid discontinued at 7-8 am day after surgery. Indwelling catheters were generally removed during day 1. If there was a need to continue the patient-controlled analgesia, though, the catheters were left in situ and removed soon after use of the analgesia stopped. All patients were encouraged to mobilize on day 1, for example, by lying on their side or sitting on the bed.

### *Sample size calculation*

The estimation of the sample size was based on a prior investigation of gynecological surgery with an ERAS protocol that had been conducted at the Faculty of Medicine Siriraj Hospital. Data from that study showed that 60% of patients were discharged within 3 days of surgery. The current work assumed that 80% of patients would be discharged after receiving simethicone on the first postoperative day. The sample size was calculated for a power expectation of 80%, with a two-sided type I error of 0.05 to detect statistical significance. Using an anticipated dropout rate of 10%, the sample size was determined to be 182 patients (91 participants per group).

### *Statistical analysis*

Data were analyzed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean and standard deviation (SD); number (n) and percentage (%); or median and interquartile range (IQR), as appropriate. Evaluation of the efficacy outcomes was based on per-protocol and modified intention-to-treat (ITT) analyses; in other words, all patients who took at least one dose of the trial medication were included in the analyses. As to patients who did not comply with the protocol, we applied the last-observation-carried-forward method for the ITT analysis. The normality of continuous data was tested using histogram plots and/or the Kolmogorov–Smirnov test of normality. Student's t-test (or the Mann-Whitney U test) and the chi-squared test (or Fisher's exact test) were used to analyze continuous and categorical data, respectively. To identify the factors associated with length of stay, univariate and multivariate logistic regressions were employed. All tests were two-tailed, and a p value $< 0.05$ was regarded as statistically significant.

## Results

A flowchart of the participants is presented in Fig. 1. Of the 182 participants who consented, 3 were excluded after assignment to the simethicone group because they had pathology reports confirming malignancy. A further 2 were removed from the control group because of injury to the bowel mucosa. The remaining 177 patients were included in the analyses. All received routine postoperative care in an ERAS setting. Half (88 women) had been assigned to chew simethicone immediately after surgery, while the other half (89 women) had been placed in the control group (no use of simethicone).

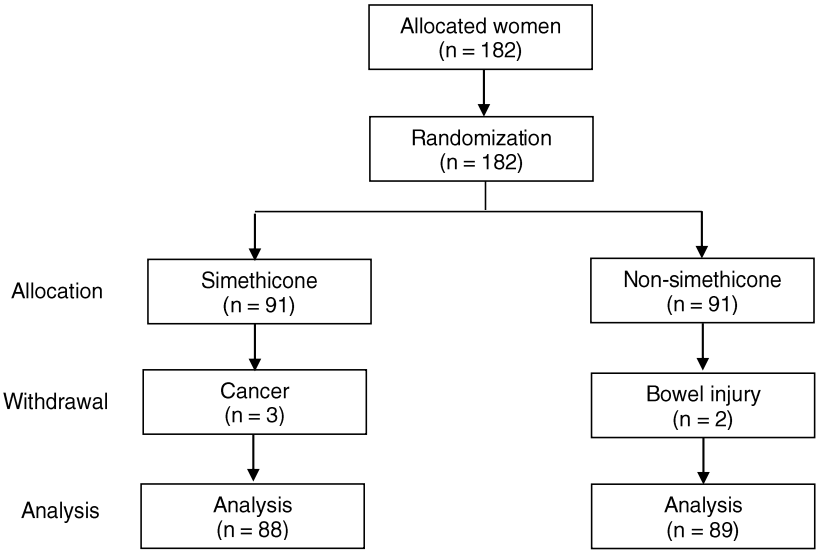


**Fig. 1.** Flow chart of participants.

The characteristics of the 182 participants are detailed in Table 1. Their ages ranged from 18 to 77 years (mean ± SD, 44.0 ± 8.3 years). Thirty-five women (19.2%) had natural menopause. The mean body mass index (BMI) was 25.1 ± 4.8 kg/m$^2$, with most participants having a BMI > 23 kg/m$^2$ (63.7%). The median (IQR) length of hospital stay was 3.0 (3, 3) days. The average nothing-per-oral (NPO) interval was 10.8 ± 2.6 hours, while the mean duration of urinary catheterization after surgery was 22.4 ± 9.6 hours. The most common gynecological disease was myoma uteri (60.4%), and the most frequent procedure was total abdominal hysterectomy with bilateral salpingo-oophorectomy (74.7%). Pfannenstiel incision was the most prevalent incision type (73.1%). Most patients received regional anesthesia (67.0%); only 18.7% had general anesthesia, and 14.3% were administered general endotracheal anesthesia with an epidural. The median estimated intraoperative blood loss was 360.7 (100.0, 462.5) mL, with 12.1% patients receiving blood transfusions. The mean operative duration was 128.6 ± 45.8 minutes.

Intraoperative complications occurred in 4 (2.1%) patients: 2 had small bowel mucosa injuries, one had bladder injury, and one had ureter injury. All were treated surgically during the primary operative procedure. Postoperatively, 49 (26.9%) patients received narcotics drugs to manage pain; 42 (23.1%) had non-steroidal inflammatory drugs (NSAIDs); 31 (17.0%) were given a combination of painkiller medications; and 60 (33.0%) did not utilize any painkiller. Antiemetics were required by 66 (36.3%) patients. Simethicone usage was noted in 102 (56.0%) patients who developed abdominal discomfort on postoperative day 2.

**Table 1.** Baseline characteristics of patients undergoing laparotomy for benign gynecological diseases.

| Baseline characteristics | Mean ± SD, or n (%), or median (interquartile range, IQR) |
|---|---|
| Age (years) | 44.0 ± 8.3 |
| ≥ 50 | 35 (19.2%) |
| Menopause | 22 (12.1%) |
| Body mass index (kg/M2) | 25.1 ± 4.8 |
| ≥ 23 | 116 (63.7%) |
| ≥ 27.5 | 53 (29.1%) |
| Length of hospital stay (days) | 3 (3, 3) |
| Intravenous fluid volume (mL) | 2,060.6 ± 781.0 |
| Duration of urinary catheterization (hours) | 22.4 ± 9.6 |
| Blood loss (mL) | 200.0 (100.0, 462.5) |
| Blood transfusion, yes | 22 (12.1%) |
| Preoperative factor | |
| Comorbidity, yes | 73 (40.1%) |
| Previous abdominal surgery, yes | 81 (44.5%) |
| ASA class 1 | 94 (51.6%) |
| Duration of NPO (hours) | 10.8 ± 2.6 |
| Benign gynecological disease | |
| Myoma | 110 (60.4%) |
| Adenomyosis | 39 (21.4%) |
| Ovarian cyst | 24 (13.2%) |
| Other | 9 (4.9%) |
| Intraoperative factor | |
| Intraabdominal adhesion, yes | 65 (35.7%) |
| Duration of operation (minutes) | 128.6 ± 45.8 |
| Type of surgery | |
| Myomectomy | 32 (17.6%) |
| Cystectomy | 6 (3.3%) |
| Salpingo-oophorectomy | 5 (2.7%) |
| TAH with BSO | 136 (74.7%) |
| Other | 3 (1.6%) |
| Type of anesthesia | |
| General | 34 (18.7%) |
| Regional | 122 (67.0%) |
| Combined | 26 (14.3%) |
| Type of incision | |
| Midline | 38 (20.9%) |
| Pfannenstiel | 133 (73.1%) |
| Maylard | 11 (6.0%) |
| Postoperative factor | |
| Pain killer, yes | 122 (67.0%) |
| Narcotic drugs | 49 (26.9%) |
| NSAIDs | 42 (23.1%) |
| Combination | 31 (17.0%) |
| Antiemetic medicine, yes | 66 (36.3%) |
| Simethicone addition | 102 (56.0%) |
| Complication | |
| Bowel injury | 2 (1.1%) |
| Bladder injury | 1 (0.5%) |
| Ureter injury | 1 (0.5%) |

Data are mean ± SD; number (n) and percentage (%); or median and interquartile range (IQR). BSO: bilateral salpingo-oophorectomy, NPO: nothing per oral, TAH: total abdominal hysterectomy

Table 2 lists the outcomes of the ITT population. The mean ± SD ages were 43.9 ± 8.1 years for the control participants, and 44.1 ± 8.4 years for the simethicone group. There was no statistically significant difference in the ages, menopausal status, or BMI values of the 2 groups. The groups had similar surgical variables: intravenous fluid volume, duration of urinary catheterization, blood transfusion volume, the type of benign gynecological disease, and the surgery duration and type. Although the proportion of participants who were discharged from the hospital within 2 days of surgery was higher for the control group than the simethicone group, there was no significant difference. Analysis using the ITT and per protocol data revealed similar results (data not shown).

The average length of hospital stay was 3 days. Patients were admitted 1-2 days before surgery, depending on their ability to optimize preoperative care. For our data analysis, we only considered the nights spent in hospital after surgery. This seemed to be more accurate, and its use eliminated any bias induced by individual patients' circumstances. The average number of postoperative days was 3.0 (3, 3) for both groups, with no statistical significance (p = 0.869). Sixteen (17.6%) control group patients were discharged within 2 days, whereas 9 (9.9%) simethicone-group patients were.

**Table 2.** Baseline parameters and outcomes of intention to treat (ITT) population.

| Parameters | Control group (n = 91) | Simethicone group (n = 91) | p value |
|---|---|---|---|
| Age (years) | 43.9 ± 8.1 | 44.2 ± 8.4 | 0.865 |
| ≥ 50 | 16 (17.6%) | 19 (20.9%) | 0.573 |
| Menopause | 12 (13.2%) | 10 (11.0%) | 0.649 |
| Body mass index (kg/M2) | 25.1 ± 4.7 | 25.1 ± 4.9 | 0.982 |
| ≥ 23 | 42 (46.2%) | 44 (48.4%) | 1.000 |
| ≥ 27.5 | 27 (29.7%) | 26 (28.6%) | 0.870 |
| Length of hospital stay | 3 (3, 3) | 3 (3, 3) | 0.869 |
| ≤ 2 day | 16 (17.6%) | 9 (9.9%) | 0.132 |
| Intravenous fluid volume (mL) | 2,044.7 ± 692.2 | 2,076.5 ± 864.4 | 0.785 |
| Duration of urinary catheterization (hours) | 23.4 ± 12.5 | 21.5 ± 5.2 | 0.190 |
| Blood loss (mL) | 200 (100, 400) | 250 (100, 500) | 0.247 |
| Blood transfusion, yes | 10 (11.0%) | 12 (13.2%) | 0.649 |
| Preoperative factor | | | |
| Comorbidity, yes | 40 (44.0%) | 33 (36.3%) | 0.290 |
| Previous abdominal surgery, yes | 44 (48.4%) | 37 (40.7%) | 0.296 |
| ASA class 1 | 46 (50.5%) | 48 (52.7%) | 0.767 |
| Duration of NPO (hours) | 10.8 ± 2.5 | 10.7 ± 2.6 | 0.784 |
| Benign gynecological disease | | | 0.432 |
| Myoma | 50 (54.9%) | 60 (65.9%) | |
| Adenomyosis | 21 (23.1%) | 18 (19.8%) | |
| Ovarian cyst | 15 (16.5%) | 9 (9.9%) | |
| Other | 5 (5.5%) | 4 (4.4%) | |
| Intraoperative factor | | | |
| Intraabdominal adhesion, yes | 30 (33.0%) | 35 (38.5%) | 0.439 |
| Duration of operation (minutes) | 128.7 ± 50.4 | 128.5 ± 41.1 | 0.983 |

**Table 2.** Baseline parameters and outcomes of intention to treat (ITT) population. (Cont.)

| Parameters | Control group (n = 91) | Simethicone group (n = 91) | p value |
|---|---|---|---|
| Type of surgery | | | 0.742 |
| Myomectomy | 18 (19.8%) | 14 (15.4%) | |
| Cystectomy | 4 (4.4%) | 2 (2.2%) | |
| Salpingo-oophorectomy | 3 (3.3%) | 2 (2.2%) | |
| TAH with BSO | 65 (71.4%) | 71 (78.0%) | |
| Other | 1 (1.1%) | 2 (2.2%) | |
| Type of anesthesia | | | 0.928 |
| General | 18 (19.8%) | 16 (17.6%) | |
| Regional | 60 (65.9%) | 62 (68.1%) | |
| Combined | 13 (14.3%) | 13 (14.3%) | |
| Type of incision | | | 0.163 |
| Midline | 24 (26.4%) | 14 (15.4%) | |
| Pfannenstiel | 61 (67.0%) | 72 (79.1%) | |
| Maylard | 6 (6.6%) | 5 (5.5%) | |
| Postoperative factor | | | |
| Pain killer, yes | 65 (71.4%) | 57 (62.6%) | 0.544 |
| Narcotic drugs | 26 (28.6%) | 23 (25.3%) | |
| NSAIDs | 24 (26.4%) | 18 (19.8%) | |
| Combination | 15 (16.5%) | 16 (17.6%) | |
| Antiemetic medicine, yes | 33 (36.3%) | 33 (36.3%) | 1.000 |
| Simethicone addition | 53 (58.2%) | 49 (53.8%) | 0.550 |
| Complication | | | 0.287 |
| Bowel injury | 2 (2.2%) | 0(0%) | |
| Bladder injury | 0 (0%) | 1 (1.1%) | |
| Ureter injury | 1 (1.1%) | 0 (0%) | |

Data are mean ± SD, number (n) and percentage (%), or median and interquartile range (IQR).
BSO: bilateral salpingo-oophorectomy, NPO: nothing per oral, NSAIDs: non-steroidal anti-inflammatory drugs, TAH: total abdominal hysterectomy

The adverse events are presented in Table 3. The most common were nausea, vomiting, abdominal or stomach discomfort, and diarrhea. Chart reviews revealed postoperative nausea in 25 (27.5%) patients. Postoperative emesis was reported for only 6 (6.6%) patients. Abdominal discomfort was noted in 6 (6.6%) patients, and diarrhea in 6 (6.6%). There were no statistical differences in the adverse effects of the 2 groups. None of the reported events were regarded as serious, and no participants withdrew from the study because of them.

Two cases of bowel injury were reported. One (1.1%) patient was diagnosed intraoperatively, with general surgery required for definitive management. The second case (1.1%) underwent repeat surgery for a right loop transverse colostomy. With the latter case, sigmoid diverticulitis and perforation were diagnosed on postoperative day 3. This followed the development of fever and abdominal pain, and the subsequent detection of an intra-abdominal collection by a computerized tomography study of the whole abdomen. With both patients, the initial gynecological procedure involved extensive dissection of the rectosigmoid off the posterior uterus because of severe adhesion. Although both of the patients with bowel complications were from the simethicone group, there was no statistical difference from the control group (p = 0.287).

**Table 3.** Adverse events of intention to treat (ITT) population.

| Adverse events | Control group (n = 91) | Simethicone group (n = 91) | p value |
|---|---|---|---|
| Overall | 24 (26.4%) | 16 (17.6%) | 0.152 |
| Nausea | 14 (15.4%) | 11 (12.1%) | 0.518 |
| Vomiting | 3 (3.3%) | 3 (3.3%) | 1.000 |
| Abdominal or stomach discomfort | 4 (4.4%) | 2 (2.2%) | 0.682 |
| Diarrhea | 4 (4.4%) | 2 (2.2%) | 0.682 |

Data are number (n) and percentage (%). Some patients had more than one adverse event.

The study revealed no significant differences between the groups in terms of their levels of patient satisfaction (p = 0.507) or their pain scores (p = 0.811; Table 4).

**Table 4.** Satisfaction and pain scores of patients undergoing laparotomy for benign gynecologic surgery.

| Factors | N | Control group (n=91) | Simethicone group (n=91) | p value |
|---|---|---|---|---|
| Patient satisfaction | 182 | 7.70±1.04 | 7.80±0.96 | 0.507 |
| Pain scores | | | | 0.811 |
| 1-3 | 2 | 1(1.1%) | 1(1.1%) | |
| 4-6 | 25 | 14(15.4%) | 11(12.1%) | |
| 7-10 | 155 | 76(83.5%) | 79(86.8%) | |

Data are mean ± SD, or number (n) and percentage (%).

The results of the univariate analysis to identify the predictive characteristics of a hospital discharge within 2 postoperative days are given in Table 5. No significant correlation was found between discharge by the end of postoperative day 2 and the following factors: age, menopausal status, BMI, intravenous fluid volume, duration of urinary catheterization, estimated blood loss, blood transfusion, perioperative factors, anesthetic method, incision type, or other postoperative factors (pain killer, antiemetic drugs, and complications).

**Table 5.** Factors associated with length of stay following benign gynecological surgery.

| Factors | Length of stay | | | p value |
|---|---|---|---|---|
| | Within Day 2 (n/N) (n=25) | More than Day 2 (n/N) (n=157) | OR (95% CI) | |
| Clinical | | | | |
| Age (years) | | | | 0.420 |
| ≥ 50 | 3 (12.0%) | 32 (20.4%) | 1.00 | |
| < 50 | 22 (88.0%) | 125 (79.6%) | 1.88 (0.53, 6.67) | |
| Menopausal status | | | | 0.319 |
| Yes | 1 (4.0%) | 21 (13.4%) | 1.00 | |
| No | 24 (96.0%) | 136 (86.6%) | 3.71 (0.48, 28.86) | |
| BMI (kg/M$^2$) | | | | 0.976 |
| ≥ 23 | 16 (64.0%) | 100 (63.7%) | 1.01 (0.42, 2.4) | |
| < 23 | 9 (36.0%) | 57 (36.3%) | 1.00 | |

**Table 5.** Factors associated with length of stay following benign gynecological surgery. (Cont.)

| Factors | Length of stay | | | p value |
|---|---|---|---|---|
| | Within Day 2 (n/N) (n=25) | More than Day 2 (n/N) (n=157) | OR (95% CI) | |
| Intravenous fluid volume (mL) | | | | 0.110 |
| ≥ 1,000 | 22 (88.0%) | 151 (96.2%) | 1.00 | |
| < 1,000 | 3 (12.0%) | 6 (3.8%) | 3.43 (0.80, 14.72) | |
| Duration of urinary catheterization (hours) | | | | 1.000 |
| ≥ 12 | 25 (100%) | 156 (99.4%) | – | |
| < 12 | 0 (0.0%) | 1 (0.6%) | | |
| Blood loss (mL) | | | | 0.066 |
| ≥ 500 | 2 (8.0%) | 43 (27.4%) | 1.00 | |
| < 500 | 23 (92.0%) | 114 (72.6%) | 4.34 (0.98, 19.19) | |
| Blood transfusion | | | | 0.319 |
| Yes | 1 (4.0%) | 21 (13.4%) | 1.00 | |
| No | 24 (96.0%) | 136 (86.6%) | 3.71 (0.48, 28.86) | |
| Preoperative factor | | | | |
| Comorbidity, no | 17 (68.0%) | 92 (58.6%) | 1.50 (0.61, 3.69) | 0.373 |
| Previous abdominal surgery, no | 11 (44.0%) | 90 (57.3%) | 0.58 (0.25, 1.37) | 0.213 |
| ASA class < 2 | 17 (68.0%) | 77 (49.0%) | 2.21 (0.90, 5.41) | 0.078 |
| Duration of NPO < 6 hours | 1 (4.0%) | 11 (7.0%) | 0.553 (0.07, 4.45) | 1.000 |
| Type of surgery | | | | 0.009 |
| Myomectomy | 10 (40.0%) | 22 (14.0%) | 1.00 | |
| Cystectomy | 2 (8.0%) | 4 (2.5%) | 1.10 (0.17, 7.03) | |
| Salpingo-oophorectomy | 1 (4.0%) | 4 (2.5%) | 0.55 (0.05, 5.57) | |
| TAH with BSO | 12 (48.0%) | 124 (79.0%) | 0.21 (0.08, 0.55) | |
| Other | 0 (0.0%) | 3 (1.9%) | – | |
| Type of anesthesia | | | | 0.225 |
| General | 4 (16.0%) | 30 (19.1%) | 1.00 | |
| Regional | 20 (80.0%) | 102 (65.0%) | 1.47 (0.47, 4.64) | |
| Combined | 1 (4.0%) | 25 (15.9%) | 0.30 (0.03, 2.86) | |
| Type of incision | | | | 0.155 |
| Midline | 3 (12.0%) | 35 (22.3%) | 1.00 | |
| Pfannenstiel | 22 (88.0%) | 111 (70.7%) | 2.31 (0.65, 8.19) | |
| Maylard | 0 (0.0%) | 11 (7.0%) | – | |
| Postoperative factor | | | | |
| Pain killer | | | | 0.289 |
| None | 9 (36.0%) | 51 (32.5%) | 1.00 | |
| Narcotic drugs | 6 (24.0%) | 43 (27.4%) | 0.791 (0.26, 2.40) | |
| NSAIDs | 3 (12.0%) | 39 (24.8%) | 0.44 (0.11, 1.72) | |
| Combination | 7 (28.0%) | 24 (15.3%) | 1.65 (0.55, 4.97) | |
| Antiemetic medicine, no | 17 (68.0%) | 99 (63.1%) | 1.25 (0.51, 3.06) | |
| Simethicone addition | 12 (48.0%) | 90 (57.3%) | 1.00 | 0.383 |
| No simethicone addition | 13 (52.0%) | 67 (42.7%) | 0.69 (0.29, 1.60) | |
| Complication, no | 25 (100%) | 152 (96.8%) | – | 1.000 |

Data were analyzed using multiple logistic regression (enter method).

The findings of a subsequent multivariate analysis are summarized in Table 6. There appeared to be an increased likelihood for early discharge of patients with a low blood loss (< 500 mL; OR 5.82 [1.20, 28.16]; p = 0.029). Interestingly, the intravenous fluid volume, ASA classification 1, and other types of surgery were not identified as significant factors.

**Table 6.** Multivariate logistic regression of factors associated with hospital discharge within 2 days of benign gynecological surgery.

| Factors | p value | Adjusted OR (95% CI) |
|---|---|---|
| Intravenous fluid volume (mL) < 1,000 | 0.121 | 3.84 (0.70, 21.01) |
| Blood loss < 500 mL | 0.029 | 5.82 (1.20, 28.16) |
| ASA class 1 | 0.412 | 1.53 (0.55, 4.26) |
| Type of surgery | | |
| Myomectomy | 0.023 | 1.00 |
| Cystectomy | 0.529 | 0.52 (0.07, 3.91) |
| Salpingo-oophorectomy | 0.539 | 0.46 (0.04, 5.40) |
| TAH with BSO | 0.002 | 0.192 (0.066, 0.557) |

Data were analyzed using multiple logistic regression (enter method). TAH with BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy.

# Discussion

Postoperative ileus is one of the reasons for a prolonged hospital stay after abdominal surgery[4, 6]. Numerous studies have evaluated pharmacological strategies and methods to reduce the occurrence of ileus. Simethicone, an antifoaming agent, has been proposed as a low-risk intervention to prevent ileus. Only 2, relatively old, randomized controlled trials demonstrated an early passage of flatus, reduced gas pain, and a decreased rate of ileus[11, 12].

The current investigation was the first to assess whether shorter hospital stays result from using simethicone to promote the return of bowel function after open benign gynecological surgery. Simethicone demonstrated no significant effect on the length of stay (p = 0.869), postoperative nausea (p = 0.518), vomiting (p =1.000), or abdominal discomfort (p = 0.682). Additionally, the simethicone and non-simethicone groups had comparable adverse events as well as similar postoperative pain and patient satisfaction levels. Our results differed from those of a study in which the patients chewed gum after completing staging surgery for gynecological malignancies. That work found that the mean length of hospital stay was significantly reduced for the patients who chewed gum compared with controls (5.9 ± 1 and 7.0 ± 1.4 days, p < 0.001)[13]. The discrepancy can be explained by differences in the study methods. In our work, the patients in the simethicone group were given only one dose of simethicone (80 mg) immediately after surgery. However, additional, variable doses of simethicone were given to patients in both the immediate-simethicone-administration and non-immediate-simethicone-administration groups, depending on patients' symptoms or as an abdominal distension prophylaxis by surgeons. Another consideration is that postoperative ileus is self-limiting. Recovery often begins in the small intestine (about 8 - 12 hours postoperatively), then the stomach (about 1 - 2 days), and finally the colon (about 3 - 5 days)[10]. Our study only assessed patients undergoing benign gynecological surgery, which is less likely to involve intense bowel manipulation. Hence, not all participants in the present work developed postoperative ileus, or the ileus may have improved by itself without the need for simethicone.

The secondary aim of this study was to identify factors influencing the duration of hospital stay. Our findings showed that an estimated blood loss below 500 mL was significantly associated with a short hospital admission (p = 0.029, OR 5.82, 95%CI 1.20,

28.16). In contrast, no statistical differences were found for many other factors. They were age, menopausal status, BMI, intravenous fluid or blood transfusion volume, duration of NPO or urinary catheterization, presence of comorbidities, previous abdominal surgery, ASA classification, type of surgery, anesthesia, or incision, painkiller usage, and postoperative complications. The results showed the lesser blood loss (< 400 ml, 90$^{th}$ percentile) was associated with a decreased hospital stay, major postoperative complications, reoperation, and readmission[14]. We assume that the undifferentiated of surgical indication, population age, and BMI may produce the same outcomes, however, further study is required to confirm this.

A retrospective review of patients undergoing open gynecological surgery with ERAS protocols revealed that a vertical midline incision, perioperative complications, malignancy, advanced stage disease, and intensive care unit admission were significantly associated with prolonged hospital stays[15]. Our results differed from those of that study. It found that 73.8% of patients were successfully discharged in 3 days or less (mean 3.5 days [3.3, 3.8]), compared with 86.8% of our patients (mean 3.0 days [3, 3]). The difference may be due to our patients having benign conditions and not undergoing lymphadenectomies or omentectomies, with midline incisions being used in only 20.9% of cases. The absence of lymphadenectomies and the much lower usage of vertical midline incisions in our study may explain why vertical midline incisions were not associated with a prolonged hospital stay.

Our results showed no significant difference in the lengths of stay for the 2 predominant types of abdominal incision used in the current investigation (Pfannenstiel and vertical midline). This result differs from a retrospective review on open gynecological surgery in the setting of an ERAS protocol[15]. We hypothesize that our results differ from that finding because all of our patients had benign conditions. By contrast, the patients in the other review had both benign and malignant conditions, and the rate of vertical incision was higher. On the other hand, our results were similar to those of a randomized controlled trial comparing abdominal hysterectomies performed by vertical midline versus low transverse incisions. It found no significant difference in the lengths of stay for the 2 incisions[16]. The similarity of our study and previous reported may be the same condition of patient and operation (simple hysterectomy).

There had several limitations of our analysis. Our study focused on the effects of simethicone, for which we employed subjective and imperfect measurements. Unlike previous studies, we chose to measure postoperative nausea, vomiting, and abdominal discomfort rather than the time to flatus or the time to passing stoo[6, 10, 13, 17]. An additional limitation was the variability of the administered doses. All of the patients in the immediate-simethicone-administration group received 80 mg of simethicone within 2 hours of their surgery. However, some patients in both groups received extra doses of simethicone (40 mg) after surgery, this was done in accordance with their surgeons' orders to stimulate the bowel function. Unfortunately, we could not control this variable. There were other factors that may have influenced the lengths of stay. These included several operators in this study (residents and gynecological surgeons), and variability in the operative techniques employed and the postoperative care provided.

Additionally, there was a lack of blinding in this study. This may have led to bias by the patients. The participants received full information about simethicone, including its efficacy and side effects, upon admission. However, a placebo could not be prepared due to limitations related to its manufacture. Unfortunately, the Department of Pharmacology of the Faculty of Medicine Siriraj Hospital can prepare drugs in capsule form, but not in tablet form. Crushed simethicone losses its efficacy and has a specific smell and taste. The use of a placebo and the blinding of the participants would have lent weight to the findings of the study.

With the advent of ERAS protocols, patients are encouraged to resume normal eating after surgery. The current work demonstrated that simethicone did not enhance bowel recovery following gynecological

surgery, and it had no effect on the length of hospital stay. Patients who were following an ERAS protocol took simethicone immediately after laparotomies for benign gynecologic procedures did not shorten the length of hospital stay.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

# The Proportion and Predicting Factors of Residual Disease after Conization of Women Diagnosed with Adenocarcinoma in Situ (AIS) in a Tertiary Center

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## ABSTRACT

**Objectives:** To investigate the proportion of residual disease after conization and the factors that significantly predict residual disease in patients diagnosed with adenocarcinoma in situ (AIS) on conization who underwent subsequent hysterectomy.

**Materials and Methods:** Medical records of patients who were diagnosed with AIS on conization during 2007-2019 were retrospectively reviewed, and the data were followed until December 2020. Demographic/clinical data, method of conization, pathology results, follow-up data, and oncologic outcomes were analyzed using descriptive statistics. Logistic regression for univariate and multivariate analyses in a stepwise model was used to identify factors that predict residual disease in hysterectomy tissue.

**Results:** A total of 149 AIS patients were evaluated for eligibility. Of those, 57 patients were excluded due to having coexisting adenocarcinoma. The remaining 92 patients were recruited. The mean age of patients was 43.4 ± 10.8 years. The most common preceding cytology was high-grade squamous intraepithelial lesion (HSIL). Subsequent hysterectomy was performed in 68 patients, and 20 (29.4%) of those were found to have residual disease. Age ≥ 50 and absence of coexisting HSIL were significant in univariate analysis, but only age ≥ 50 years [adjusted odds ratios (aOR): 3.667, 95% confidence interval (CI) 1.224-10.980, p = 0.017] was identified as an independent predictor of residual disease in multivariate analysis. The median follow-up time was 58.4 months, and all 92 patients were alive without disease.

**Conclusion:** The proportion of residual disease in patients diagnosed AIS was 29.4%. Age ≥ 50 years was identified as the only independent predictor of residual disease.

**Keywords:** cervix, adenocarcinoma in situ, conization, hysterectomy, residual diseases.

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# *สัดส่วนและปัจจัยทำนายรอยโรคที่เหลือภายหลังการตัดปากมดลูกเป็นรูปกรวย ในสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมา ในสถานพยาบาลตติยภูมิ*

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## *บทคัดย่อ*

***วัตถุประสงค์****: เพื่อศึกษาสัดส่วนของการมีรอยโรคที่เหลืออยู่จากผลพยาธิวิทยาของการตัดมดลูก ในสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาจากการตัดปากมดลูกเป็นรูปกรวย และเพื่อประเมินปัจจัยทำนายการมีรอยโรคที่เหลืออยู่ดังกล่าว*

***วัสดุและวิธีการ****: ทำการเก็บข้อมูลย้อนหลังของสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาจากการตัดปากมดลูกเป็นรูปกรวย ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2550 ถึง 31 ธันวาคม พ.ศ. 2562 และข้อมูลของการตรวจติดตามจนถึงวันที่ 31 ธันวาคม พ.ศ. 2563 นำข้อมูลต่างๆ ได้แก่ ข้อมูลทั่วไป วิธีการตัดปากมดลูกเป็นรูปกรวย ผลทางพยาธิวิทยา ผลการตรวจติดตาม และผลลัพธ์ทางมะเร็งวิทยานรีเวช มาวิเคราะห์ด้วยสถิติเชิงพรรณนา และสำหรับปัจจัยทำนายการมีรอยโรคที่เหลืออยู่ใช้การวิเคราะห์การถดถอย*

***ผลการศึกษา****: จากสตรีทั้งหมด 149 คน ที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาในช่วงระยะเวลาดังกล่าว สตรี 57 คน ถูกคัดออกเนื่องจากมีมะเร็งปากมดลูกชนิดอะดีโนคาร์ซิโนมาร่วมด้วย ดังนั้นได้สตรีที่เข้าเกณฑ์งานวิจัยจำนวน 92 คน พบว่ามีค่าเฉลี่ยของอายุของสตรี เท่ากับ 43.4 ± 10.8 ปี ในสตรีที่มีผลเซลล์วิทยาปากมดลูกนำมาก่อนส่วนใหญ่พบเป็นชนิด high-grade squamous intraepithelial lesion (HSIL) มีสตรีได้รับการตัดมดลูกภายหลังการตัดปากมดลูกเป็นรูปกรวย จำนวน 68 คน ในจำนวนนี้มีสตรี 20 คน ตรวจพบรอยโรคที่เหลืออยู่ คิดเป็นร้อยละ 29.4 จากการวิเคราะห์ตัวแปรเดี่ยว (univariate analysis) พบว่า อายุมากกว่าหรือเท่ากับ 50 ปี และรอยโรคภายในเยื่อบุปากมดลูกชนิดสแควมัสขั้นสูงที่พบจากการตัดปากมดลูกเป็นรูปกรวยมีความสัมพันธ์กับการตรวจพบรอยโรคที่เหลืออยู่อย่างมีนัยสำคัญทางสถิติ และเมื่อทำการวิเคราะห์ตัวแปรพหุ (multivariate analysis) พบว่า ปัจจัยทำนายรอยโรคที่เหลืออยู่ คือ อายุมากกว่าหรือเท่ากับ 50 ปี จะเพิ่มโอกาสการมีรอยโรคที่เหลืออยู่ถึง 3.667 เท่า (95% CI 1.224-10.980, p = 0.017]) ระยะเวลาการตรวจติดตามที่ค่ามัธยฐาน 58.4 เดือน [interquartile range 26.3-100.7] พบว่า สตรีทั้ง 92 คน มีชีวิตอยู่โดยปราศจากโรค*

***สรุป****: สตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนจากการตัดปากมดลูกเป็นรูปกรวย เมื่อรับการตัดมดลูกพบรอยโรคที่เหลืออยู่ คิดเป็นสัดส่วนร้อยละ 29.4 และอายุมากกว่าหรือเท่ากับ 50 ปี เป็นปัจจัยทำนายการมีรอยโรคที่เหลืออยู่*

***คำสำคัญ:*** *ปากมดลูก, รอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมา, การตัดปากมดลูกเป็นรูปกรวย, การตัดมดลูก, การมีรอยโรคที่เหลืออยู่*

## Introduction

Cervical adenocarcinoma in situ (AIS) is a pathology diagnosis on conization procedure that attempts to excise the whole transformation zone in a single piece of conization specimen with a length of ≥ 10 mm to ensure no coexisting invasive adenocarcinoma. Either cold knife conization (CKC) or loop electrical excision procedure (LEEP) can be used[1-3]. AIS is recognized as a precancerous lesion of cervical adenocarcinoma. Since they are similar in morphology and oncogenic human papillomavirus types, coexisting AIS was found in most cervical adenocarcinoma cases, and patients with AIS were younger than those with adenocarcinoma by at least 5 years[2,4]. AIS normally hides in endocervical crypts, and 10-15% present as "skip lesion", which is condition in which AIS is separated by normal mucosa ≥ 2 mm[3]. This phenomenon is the cause of residual disease being found in up to 50% of post-conization hysterectomy specimens[5-7]. In addition, the recurrence rate in conservative treatment after free margin conization was 2.6-3%, and the rate increased to 17-19.4% in positive margins cases[2,4]. For this reason, the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 and the Society of Gynecologic Oncology (SGO) 2020 recommend hysterectomy as the standard of treatment for women who do not need to remain fertile. However, in cases where fertility must be preserved, free margin conization and negative disease on endocervical curettage must be combined with close surveillance until the completion of childbearing[1,2].

The emergence of cervical cancer screening programs has led to a decrease in the incidence of cervical squamous precancerous lesion. On the contrary, the incidence of AIS has increased, and the mean age of patients at diagnosis was reported to be 35-37 years[2]. A current lifestyles trend in many countries is delayed childbearing, which increases the need for fertility-sparing surgical treatments. Accordingly, the primary aim of this study was to investigate the proportion of residual diseases after conization, and the secondary aim was to determine factors that independently predict residual disease in patients diagnosed with AIS on conization who underwent subsequent hysterectomy. Along with, to assess the oncologic outcomes of both definite hysterectomy and fertility conserved patients.

## Materials and Methods

After receiving study approval from the Siriraj Institutional Review Broad of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA Si 009/2020), medical data of patients diagnosed with AIS on conization from January 2007 to December 2019 were retrospectively reviewed, and the data were followed until December 2020. Demographic and clinical data, preceding cervical cytology results, conization methods, pathological description of conization and hysterectomy specimens, post-surgical management, and follow-up data were collected, recorded, and analyzed. Written informed consent was not obtained due to the anonymous retrospective nature of this study.

Cervical cytology results were reclassified according to the Bethesda 2014 system. Conization tissue was inked prior to serial section and entirely submitted for microscopic evaluation. Histopathology diagnosis was made by gynecologic pathologists. Cone margins were divided into ectocervical and endocervical margins. Positive margin was defined as presence of squamous intra-epithelial lesions (SIL) or AIS at cone margins or ≤ 1 mm margin distance. According to histopathology criteria of the World Health Organization (WHO) 2014 classification, precancerous lesions was classified as either SIL and AIS. SIL was then further subclassified into low-grade SIL (LSIL) or high-grade

SIL (HSIL). In subsequent hysterectomy specimens, the "residual diseases" was defined as the presence of SIL, AIS, or invasive cervical cancer. In follow-up period, women were evaluated by pelvic examination together with cytology with/without high-risk human papillomavirus (HPV) testing every 6 months for 5 years and then every 1 year. Threshold for colposcopy was positive high-risk HPV or abnormal cytology at index atypical squamous cells of undetermined significance (ASC-US) or worse. Recurrent disease was defined as the histopathologic finding of SIL, AIS, or invasive cervical cancer at least 6 months after hysterectomy or conization.

Data were analyzed using SPSS Statistics software version 18.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize baseline characteristics, such as demographic and clinical information, preceding cytology results, conization methods, subsequent management procedures, histopathology, residual diseases, and recurrent disease. Results were given as number and percentage. Continuous data was presented as median and interquartile range (IQR). Logistic regression analysis was used to identify independent predictors of residual disease in post-hysterectomy tissue. Univariate analysis was presented as odds ratio (OR) with 95% confidence intervals (CI) and multivariate analysis was presented as stepwise logistic regression. A p value (two-sided) less than 0.05 was considered to be statistically significant.

## Results

A total of 2,093 women underwent conization at the Division of Gynecologic Oncology of the Department of Obstetrics and Gynecology during the study period. Of these, 149 medical records of patients with AIS on conization specimen were reviewed. The AIS patients with AIS on conization specimen were reviewed. The AIS patient recruitment process, including conization, subsequent management, and pathology results, is shown by flow diagram in Fig. 1. After excluding 57 patients for histopathologic diagnosis of AIS with concurrent adenocarcinoma, the remaining 92 patients were included for analysis. Thirty-two patients (34.8%) had positive cone margins. Of those, 2/13 of CKC (15.4%), and 30/79 of LEEP (37.9%) had positive margins. In 26 patients who positive cone margins had proportion of residual AIS and adenocarcinoma was 23.1% and 7.7%, respectively. But in 42 patients who negative cone margins were 16.7% and 4.8%, respectively.

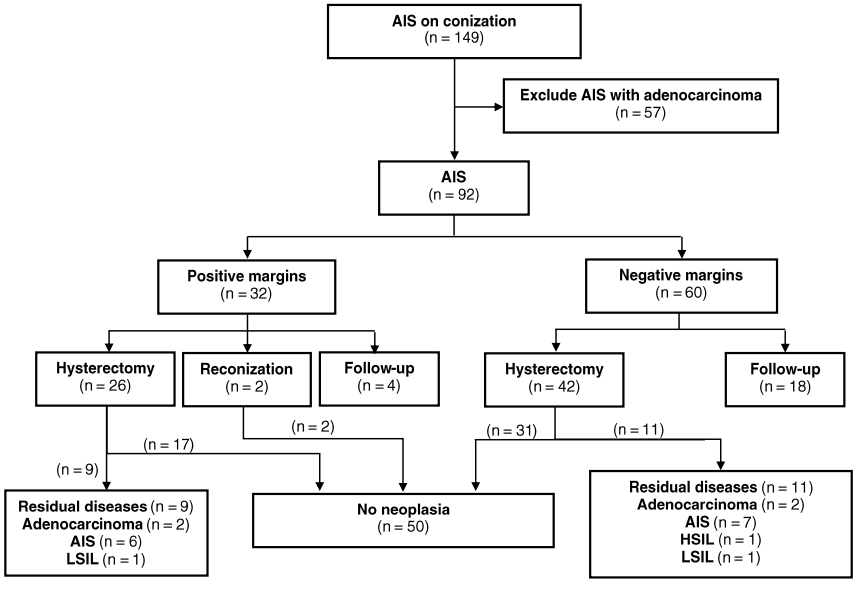


**Fig. 1.** Flow diagram demonstrating the recruitment process of patients with adenocarcinoma in situ on conization, and subsequent management with pathology results. AIS: adenocarcinoma in situ, HSIL: high-grade squamous intraepithelial lesion, LSIL: low-grade squamous intraepithelial lesion.

Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with AIS on conization are shown in Table 1. The mean age of patients was 43.4 ± 10.8 years. The median parity was 2 (IQR 1-2). The median body mass index was 22.4 kg/m$^2$ (IQR 20.4-24.7). Seventy-one women (77.2%) were premenopausal. Eighty-seven patients had preceding cervical cytologies. The most common preceding cervical cytology was HSIL. Median time from conization to subsequent hysterectomy in 68 women was 10 weeks (IQR 8-12). Of these, 20 of 68 patients (29.4%) had residual diseases.

**Table 1.** Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with adenocarcinoma in situ on conization.

| Characteristics/ finding/ outcomes | Values |
|---|---|
| Preceding cytology | |
| NILM | 2 (2.2%) |
| ASC-US | 5 (5.4%) |
| LSIL | 6 (6.5%) |
| ASC-H | 5 (5.4%) |
| HSIL | 35 (38.0%) |
| AGC-NOS | 5 (5.4%) |
| AGC-FN | 6 (6.5%) |
| AIS | 13 (14.1%) |
| Adenocarcinoma | 10 (10.9%) |
| Punch biopsies without cytology | 1 (1.1%) |
| No data | 4 (4.3%) |
| Conization method | |
| Cold knife conization | 13 (14.1%) |
| Loop electrosurgical excision procedure | 79 (85.9%) |
| Conization depth (mm) | 10.3 (7.0-14.0) |
| Lesion size (quadrants) | |
| 1 | 14 (15.2%) |
| 2 | 19 (20.7%) |
| 3 | 6 (6.5%) |
| 4 | 18 (19.6%) |
| No data | 35 (38.0%) |
| Coexisting squamous intraepithelial lesion | |
| None | 35 (38.0%) |
| LSIL | 3 (3.3%) |
| HSIL | 54 (58.7%) |
| Conization margin | |
| Free margins | 60 (65.2%) |
| Positive ectocervical margin | 8 (8.7%) |
| Positive endocervical margin | 24 (26.1%) |
| Disease at margins (n=32) | |
| LSIL | 1 (3.1%) |
| HSIL | 7 (21.9%) |
| AIS | 15 (46.9%) |
| AIS and HSIL | 9 (28.1%) |

**Table 1.** Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with adenocarcinoma in situ on conization. (Cont.)

| Characteristics/ finding/ outcomes | Values |
|---|---|
| Pathology of subsequent hysterectomy (n = 68) | |
| No residual disease | 48 (70.6%) |
| Residual LSIL | 2 (2.9%) |
| Residual HSIL | 1 (1.5%) |
| Residual AIS | 13 (19.2%) |
| Adenocarcinoma | 4 (5.9%) |
| Hemoglobin (g/dL) | 12.7 (12.0-13.5) |
| Hematocrit (%) | 38.9 (36.8-41.2) |
| Platelet count (/μL) | 267,500 (227,000-301,750) |
| White blood cell count (/μL) | 6,805 (5,680-8,368) |
| Neutrophil count (/μL) | 4,002 (3,046-4,844) |
| Lymphocyte count (/μL) | 2,154 (1,716-2,604) |
| Neutrophil/lymphocyte ratio | 1.8 (1.5-2.4) |

Data are presented as number (percentage) or median (interquartile range). AIS: adenocarcinoma in situ, AGC-FN: atypical glandular cells, favor neoplasia, AGC-NOS: atypical glandular cells, not otherwise specified, ASC-H: atypical squamous cell, cannot exclude HSIL, ASC-US: atypical squamous cells of undetermined significance, HSIL: high-grade squamous intraepithelial lesion, LSIL: low-grade squamous intraepithelial lesion, NILM: negative for intraepithelial lesions or malignancy

Univariate and multivariate analysis for predictive factors independently associated with residual disease in subsequent hysterectomy specimens is shown in Table 2. Conization methods, length of conization of ≥ 10 mm, and positive cone margins were not found to be significantly associated with residual diseases. Multivariate analysis showed that age of ≥ 50 years was to be the only one independent predictor of residual diseases with an adjusted OR of 3.667 (95%CI 1.224-10.980, p = 0.017) with a statistical power of 65%.

**Table 2.** Analysis for factors that significantly predict residual disease in 68 patients diagnosed adenocarcinoma in situ on conization who underwent subsequent hysterectomy.

| Variables | Residual disease n (%) | Univariate | Multivariate |
|---|---|---|---|
| | | OR [95%CI], p value | OR [95%CI], p value |
| Age (years) | | | |
| < 50 (n = 45) | 9 (20.0%) | Reference | Reference |
| ≥ 50 (n = 23) | 11 (47.8%) | 3.667 [1.224-10.980], 0.017 | 3.667 [1.224-10.980], 0.017 |
| Coexisting HSIL | | | |
| No (n = 33) | 14 (42.4%) | Reference | |
| Yes (n = 35) | 6 (17.1%) | 0.281 [0.092-0.859], 0.022 | - |
| Conization method | | | |
| LEEP (n = 58) | 17 (29.3%) | Reference | - |
| CKC (n = 10) | 3 (30.0%) | 0.967 [0.223-4.191], 1.000 | |
| Conization length (mm) | | | |
| <10 (n = 29) | 8 (27.6%) | Reference | - |
| ≥10 (n = 39) | 12 (30.8%) | 0.857 [0.297-2.476], 0.776 | |
| Disease at conization margins | | | |
| Negative (n = 42) | 11 (26.2%) | Reference | - |
| Positive (n = 26) | 9 (34.6%) | 1.492 [0.516-4.311], 0.459 | |

OR: odds ratio, CI: confidence interval, CKC: cold knife conization, HSIL: high-grade squamous intraepithelial lesion, LEEP: loop electrosurgical excision procedure

Median follow-up time was 58.4 months (IQR 26.3-100.7). Recurrent vaginal HSIL was found in one patient at 20 months after laparoscopic total hysterectomy. The recurrent lesion was successfully treated by laser ablation. No disease recurrence was observed in 24 patients who did not undergo hysterectomy. All 92 patients were alive and disease-free at the end of the follow-up in December 2020.

## Discussion

The current study showed the proportion of residual SIL/AIS/adenocarcinoma in patients who diagnosed with AIS on conization and who underwent postconization hysterectomy to be 29.4%. Negative cone margins demonstrated residual invasive disease in 4.8%. Age of ≥ 50 years and absence of co-existing HSIL were the factors significantly associated with increased risk of residual disease in univariate analysis, but age of ≥ 50 was found to be the only independent predictor of residual disease in multivariate analysis.

The proportion of positive cone margins in AIS patients was reported to be 27.5-45%, which was consistent with the findings of the present study[4-13]. The proportion of positive cone margins depends on various factors, such as definition of positive cone margins, methods of conization, and length of cone specimens. In this study, we used the same definition of positive cone margins as used by Kietpeerakool et al; however, most studies defined positive cone margins as the presence of AIS at the cone margins or AIS close to < 1 mm from the cone margins[7, 9, 12]. Alternatively, the other authors did not clearly describe how they defined positive cone margins[6, 8, 10].

In the present study, we found more positive cone margins in women treated with LEEP compared to those treated by CKC (37.9% vs. 15.4%, respectively) that consistent with other studies[4, 5, 9, 12, 13, 14]. A study from the University of Texas MD Anderson Cancer Center reported the proportion of positive cone margin AIS to be 37.8%, of which 30 were from 62 LEEP (48.4%) and 35 were from 110 CKC procedure (31.8%) (p = 0.017); however, they did not mention the length of cone specimens[9]. In contrast, Munro et al reported positive cone margin in 27.5% of patients, and the proportions in the LEEP and CKC procedures were 31.8% and 25%, respectively (p = 0.432). The length of conization specimens was reported to be significantly longer in the CKC group than in the LEEP group (16.1 mm vs. 10.7 mm, p < 0.001)[12]. Keitpeerakool et al found the average cone length from LEEP and CKC to be 9.5 mm and 16.3 mm, respectively, and LEEP had a significant higher proportion of positive cone margins compared to CKC (56.8% vs. 26.1%, respectively, p = 0.02)[5]. Young et al reported proportions of AIS positive cone margins of 50% for other conization methods, and 31% for CKC (p = 0.013). In contrast, another study found no significant difference in the length of cone specimens between the other conization methods and CKC methods (14.1 mm vs. 14.2 mm, respectively)[13]. A meta-analysis reported the proportion of positive cone margins to be 38.1%, and the proportions from the LEEP and CKC procedures were 51% and 30%, respectively[4]. A recent meta-analysis of 18 studies showed the proportion of positive cone margins after LEEP to be higher than after CKC (44% and 29%, respectively) (OR 1.55; 95%CI 1.34-1.80)[14]. That group also found the proportion of residual AIS/adenocarcinoma in subsequent reconization to be 9.1%, and in hysterectomy to be 11% (p > 0.05), and there was no significant difference in the recurrence rate between these two methods[14]. The current study and previous studies failed to address association of conization methods and proportion of residual or recurrent diseases[4,12,14]. Thus, all conization methods were not preferred in AIS and the length of cone was accepted to be more important than methods of conization[1-3].

The SGO reported the proportion of residual AIS and adenocarcinoma in postconization and received second excision specimens in cases with negative cone margins to be 20% and 2%, respectively. This proportion increase to 53% and 6%, respectively, in case with positive cone margins[2]. In 2014, a meta-analysis of 35 studies was conducted, with the enrollment of 2,125 patients diagnosed with AIS by conization. Subsequent repeat conization or hysterectomy was performed in 965 of those patients. Regarding cone margin status, residual AIS and adenocarcinoma in negative cone margins cases was found in 16.5% and 0.6% of patients,

respectively. In positive cone margin cases, residual AIS and adenocarcinoma was found in 49.3% and 5.9% of cases, respectively[4]. Keitpeerakool et al revealed a prevalence of residual AIS/HSIL in second excision specimens of 33%, and there was no case of carcinoma. They advocated positive neoplastic epithelium at the cone margin to be a strong predictor of residual AIS/HSIL ($p < 0.001$)[5]. Similarly, a study of 298 AIS patients undergoing second excision procedures found that patients who had positive cone margins had residual AIS in 56% of cases, and had adenocarcinoma in 12% of cases, whereas patients with negative cone margins had residual AIS in 20% of cases and had adenocarcinoma in 2% of cases (both comparisons $p < 0.001$)[15]. In contrast, the present study found the proportion of residual AIS/SIL/adenocarcinoma in postconization hysterectomy specimens to be as high as one-third (29.4%), and cone margins were not found to be associated with residual disease. This may be because of small number of participants for determining significant difference of margin status. Moreover, the proportion of residual carcinoma in postconization hysterectomy specimens was as high as 4.8%, even with negative cone margins.

The rate of coexisting SIL and AIS in the current study was consistent with the findings reported from previous studies (37.2-78.2%)[5, 8, 10, 12, 13, 15-18]. Furthermore, we found the absence of coexisting HSIL to be a significant predictor of residual diseases in univariate analysis. In contrary to the study of Tierny et al, they found coexisting SIL in 37.2% of AIS patients, and found no significant correlation with residual AIS/adenocarcinoma in re-excision specimens[15]. Compared with data from studies in conservative treatment, the author found that conization methods, positive cone margins, cone length more than 10 mm were not statistically correlated with persistent/recurrent of diseases[17, 18]. They found the age of > 30 years and absence of coexisting SIL to be risk factors for persistent/recurrent diseases with OR of 2.16 (95%CI 1.09-4.27), and 3.21 (95%CI 1.48-6.90), respectively[17]. Another study in 71 patients that receiving conservative treatment reported a proportion of coexisting SIL of 57.7%, and higher recurrent AIS in patients without coexisting SIL compared to those with coexisting SIL (17% vs. 2%, respectively, $p = 0.043$)[18]. The reasons that may explain the favorable effects of coexisting SIL include the fact that SIL lesions can easily be detected with screening program, and colposcopic criteria has been established to improve the detection of AIS before more aggressive pattern or migration of AIS into upper endocervical canal or beyond. Another reason is because SIL lesions are typically located mainly at the ectocervical area and might guide clinicians to perform large cone specimens.

Previous studies reported a median or mean age of AIS patients of 29-45 years[2,4]. The mean age at diagnosis in the current study was 43.4 years, which was consistent with previous findings from Thailand (45.1 years) and Korea (42 years)[5,10]. Age at diagnosis was reported to be younger in Western countries. Possible explanations for this difference include: (i) sexual activity is initiated later in Asians, and (ii) high-risk HPV genotypes in Asian patients, such as HPV 52, 58, and 66, may be less virulent than high-risk genotypes in Western countries. Unfortunately, the preservative treatment for fertility desire is not an issue because the mean age at diagnosis and the age associated with the increased residual AIS/SIL/adenocarcinoma in postconization hysterectomy are both out of reproductive period.

The strengths of this study used clearly definition of positive margin diseases, and recurrent disease types. Moreover, this study included only the participants undergoing hysterectomy for analyzing residual diseases to ensure diagnosis of all skip lesions. The limitations of this study included its retrospective design, quit not large sample size, and the lack of HPV genotyping data.

HPV genotyping or methylation profiles simultaneous at the time of conization should be further study. This information would help to predict residual diseases, which would facilitate triage of patient to undergo hysterectomy or safe uterine preservation. Furthermore, the virulence of the HPV types could help to estimate the time to recurrence in patients with

conservative treatment, which may have an influence on time of conception or time of definite radical surgery.

## Conclusion

In conclusion, one-third of study patients had residual diseases. Age ≥ 50 years and absence of co-existing HSIL were factors significantly associated with increased risk of residual disease, but age ≥ 50 was the only independent predictor of residual disease. Negative cone margin was found not to ensure the absence of invasive disease. As such, women with AIS who have a strong desire to preserve their fertility and agree to accept the risk of residual disease can be conservatively treated by cervical conization and continuous monitoring. Hysterectomy can then be performed when these women complete childbearing.


## Acknowledgement

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## GYNAECOLOGY

# Urological Injuries during Gynecologic Surgery at Songklanagarind Hospital

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## ABSTRACT

**Objectives:** To determine the incidence of urological injuries during gynecologic surgeries, and identify the risk factors associated with urological injuries, management and outcome after repair of urological injuries.

**Materials and Methods:** A retrospective case-control study of women who underwent gynecologic surgeries at Songklanagarind hospital from January 2006 to December 2020. The cases with urological injury were identified and analyzed for incidence, risk factors, management and outcome after repair of urological injuries. Demographic and clinical parameters were analyzed using multiple conditional logistic regression to clarify the determinate. A p value of $< 0.05$ was considered statistically significant.

**Results:** There were 125 cases (0.66%) of urological injuries, from a total of 19,003 gynecological surgery cases. The incidence of bladder, ureteric and combined bladder and ureteric injuries were 0.42%, 0.19% and 0.04%, respectively. A total of 117 cases with complete data was analyzed. Previous myomectomy, level of surgeon, the presence of dense pelvic adhesion, and large tumor size were significant risk factors for urological injuries ($p < 0.05$). The management of urological injuries was successful in 116 patients (99.1%).

**Conclusion:** Bladder injury was the most common urinary tract injury during gynecologic surgery. Previous myomectomy, level of surgeon, the presence of dense pelvic adhesion, and large tumor size were significant risk factors.

**Keywords:** bladder injury, ureteric injury, urologic complication, gynecologic surgery, risk factor.

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# *การบาดเจ็บต่อระบบทางเดินปัสสาวะจากการผ่าตัดทางนรีเวชที่โรงพยาบาลสงขลานครินทร์*

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***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อศึกษาอุบัติการณ์การบาดเจ็บต่อระบบทางเดินปัสสาวะจากการผ่าตัดทางนรีเวชที่โรงพยาบาลสงขลานครินทร์ ระบุปัจจัยเสี่ยงที่มีความสัมพันธ์ต่อการเกิดการบาดเจ็บต่อระบบทางเดินปัสสาวะ และศึกษาวิธีการรักษาและผลของการรักษาต่อการบาดเจ็บที่เกิดขึ้นกับระบบทางเดินปัสสาวะ*

***วัสดุและวิธีการ:*** *การศึกษาวิจัยแบบย้อนหลัง โดยเก็บข้อมูลจากเวชระเบียนของสตรีที่ได้รับการผ่าตัดทางนรีเวชที่โรงพยาบาลสงขลานครินทร์ ตั้งแต่เดือนมกราคม พ.ศ. 2549 ถึงธันวาคม พ.ศ. 2563 เพื่อระบุอุบัติการณ์ของการบาดเจ็บต่อระบบทางเดินปัสสาวะ วิเคราะห์ข้อมูลเพื่อระบุปัจจัยเสี่ยงที่มีความสัมพันธ์ต่อการเกิดการบาดเจ็บต่อระบบทางเดินปัสสาวะ และศึกษาวิธีการรักษาและผลของการรักษาต่อการบาดเจ็บที่เกิดขึ้นกับระบบทางเดินปัสสาวะ โดยกำหนดค่า p value < 0.05 ถือว่ามีนัยสำคัญทางสถิติ*

***ผลการศึกษา:*** *ผู้ป่วยที่เข้ารับการผ่าตัดทางนรีเวชทั้งหมด 19,003 คน เกิดการบาดเจ็บต่อระบบทางเดินปัสสาวะ 125 คน (ร้อยละ 0.66) โดยอัตราการบาดเจ็บต่อกระเพาะปัสสาวะพบร้อยละ 0.42 อัตราการบาดเจ็บต่อท่อปัสสาวะพบร้อยละ 0.19 และอัตราการบาดเจ็บต่อกระเพาะปัสสาวะร่วมกับท่อปัสสาวะพบร้อยละ 0.04 สามารถเก็บข้อมูลจากเวชระเบียนได้ครบจำนวน 117 คน เพื่อนำมาวิเคราะห์ข้อมูล พบว่าปัจจัยเสี่ยงที่มีนัยสำคัญต่อการบาดเจ็บของระบบทางเดินปัสสาวะ ได้แก่ เคยผ่าตัดเนื้องอกมดลูก ความเชี่ยวชาญของแพทย์ผ่าตัด ภาวะพังผืดในอุ้งเชิงกราน และขนาดของเนื้องอก ผลการผ่าตัดแก้ไขพบว่าประสบความสำเร็จจำนวน 116 คน (ร้อยละ 99.1)*

***สรุป:*** *กระเพาะปัสสาวะเป็นอวัยวะในระบบทางเดินปัสสาวะที่พบการบาดเจ็บได้บ่อยที่สุดจากการผ่าตัดทางนรีเวช โดยปัจจัยเสี่ยงที่มีนัยสำคัญต่อการบาดเจ็บของระบบทางเดินปัสสาวะ ได้แก่ เคยผ่าตัดเนื้องอกมดลูก ความเชี่ยวชาญของแพทย์ผ่าตัด ภาวะพังผืดในอุ้งเชิงกราน และขนาดของเนื้องอก*

***คำสำคัญ:*** *การบาดเจ็บของกระเพาะปัสสาวะ, การบาดเจ็บของท่อไต, ภาวะแทรกซ้อนระบบปัสสาวะ, การผ่าตัดทางนรีเวช, ปัจจัยเสี่ยง*

## Introduction

Female genital organs and urinary tracts are anatomically as well as embryogenic related. Therefore, gynecological surgeries can sometimes create an injury to the organs in the urinary system. Worldwide studies have shown that urological injuries, from gynecological surgery, range from 0.2% to 1.34%[1-5]. A previous study in Thailand reported the incidence of urinary tract injuries from gynecological procedure as being 0.3%[6]. The bladder was the most common site of injured organ at 0.18%, followed by the ureter at 0.083%, and the last was combined bladder and ureter injuries at 0.014%[2, 6, 7]. In addition of most common site of injury, bladder injuries are easier to detect during operation than ureteral injuries. Hence, it is possible to treat the injury in a concurrent procedure, leading to a successful outcome after primary repair. A previous study demonstrated a high success rate up to 88% of concurrent surgical repair of the urinary tract injuries caused by gynecological and obstetric procedure that were intraoperatively detected[2]. A small percentage of patients experienced complications after treatment such as sepsis and death at 8% and 4%, respectively[2]. Injuries to the ureters are more complicated and might involve late detection. Patients may present with symptoms of fever, back pain, vaginal discharge or non-specific symptoms[2]. Long-term consequences: such as, urogenital fistula, ureteric stenosis, or renal function loss can lead to difficult and complication in management; requiring longer hospital stays and also increasing the hospitals expenses[6-8].

There are different types of gynecological surgeries, which include abdominal, vaginal, and laparoscopic surgeries. Among these route, abdominal hysterectomy, whether benign or malignancy, are the most common that lead to urinary tract injuries[3,9]. Recent studies have found that the risk factors which increase urinary tract injuries were from ovarian cancer operations, patients with history of pelvic surgeries, excessive blood loss during operation, pelvic adhesions, endometriosis and large uterine size[2, 6, 10, 11].

There are abundant gynecological surgeries each year at Songklanagarind hospital, which is a tertiary and referral-based hospital in Southern, Thailand. Some gynecological surgeries were found to have intraoperative complications, including injury to the urinary system, gastrointestinal tracts, or vascular system. However, the precise incidence of urinary tract injures were difficult to ascertain from the literature, as they are dependent on many factors, such as the setting, different types of procedures, and the complexity of gynecological conditions. Furthermore, there was a lack of the data, including factors contributing to urologic injuries and outcome after treatment in our setting. Hence, we aimed to study the incidence of urinary tract injuries from gynecological procedures, to identify risk factors related to urinary tract injuries. Moreover, management after injury and outcomes were collected for providing information to counsel patients. In addition, the findings may help gynecologists to complete preoperative evaluations and help in the early detection of urinary tract complications.

## Materials and Methods

This was a retrospective case control study. The study was approved by the ethics committee of the institutional research board (IRB) of the Faculty of Medicine, Prince of Songkla University (REC 63-142-12-4).

The medical records of all women who underwent gynecologic surgeries from January 2006 to December 2020, in Songklanagarind hospital were reviewed. The cases were identified as patients who were diagnosed with urological injuries, including bladder, ureteric or combined bladder and ureteric injuries, detected intraoperatively or postoperatively. All charts of cases were reviewed, except charts with inadequate data. The control group was recruited from the hospital's computerized database by matching the same surgical procedure, indication and surgical date at a 1:4 of case-to-control ratio and performed by a computer-generated matching program. Demographic data regarding patient's age, body mass index, co-morbidities, previous pelvic surgeries, previous pelvic irradiation, pelvic infection, and diagnosis were obtained. Procedure related data: including indication for surgery, type of

operation, level of primary surgeon, tumor size, presence of pelvic adhesions, duration of procedure, intra-operative blood loss, intra-operative and post-operative urological injuries, and length of hospital stay were reviewed from the patient' charts. In the case group, the type of urological injuries, types of surgical repair and results after surgical repair was reviewed thoroughly.

Statistical analysis was performed using R-version 4.0.3. Descriptive data was expressed as number, percentages, median and inter quartile range (IQR; Q1, Q3) for continuous variables. Student's t-test and Wilcoxon rank-sum test were used to analyze the difference in continuous variables. Pearson's chi-squared test and Fisher's exact test were used to analyze categorical variables. Multiple conditional logistic regression analysis was used to determine the association of potential risk factors with secondary outcome variables, and to estimate adjusted odds ratio (OR) along with their 95% confidence interval (CI). Univariate analysis was first performed to identify any potential predictor variables. Variables with a p value < 0.2, according to univariate analysis and those considered to be clinically relevant were included in the multiple conditional logistic regression analysis to determine any independent predictors of the secondary outcome variables. All variables included in the final model had a variance inflation factor (VIF) of less than 2. A p value of < 0.05 was considered statistically significant.

## Results

During the period of study, 2006 to 2020, there were 19,003 patients who underwent gynecologic surgeries, with the incidence of overall urologic injuries being 0.66% (125 patients). The incidence of bladder injury, ureteric injury and combined bladder and ureteric injuries were 0.42%, 0.19% and 0.04%, respectively. There were 8 cases for which the data had incomplete records; therefore, a total of 117 patients were eligible and analyzed in this study. Of the 117 patients, 72 patients (61%) had bladder injury, followed by ureteric injury in 37 patients (32%) and combined ureter and bladder injuries in 8 patients (7%).

Demographic data of urological injury cases and the control group are shown in Table 1. The median (IQR) age of cases was 48 years. Body mass index was found to be of significant difference between the groups, which was higher in the control group.

**Table 1.** Demographic data of cases with and without urological injuries.

| Characteristics | Cases (n = 117) | Control (n = 468) | p value |
|---|---|---|---|
| Age (years) | 48 (42, 56) | 49 (44, 58) | 0.073 |
| Body mass index (kg/m$^2$) | 23.3 (20.8, 26.1) | 24.4 (21.6, 27.5) | 0.012 |
| Previous pelvic surgery | 58 (49.6) | 187 (39.9) | 0.075 |
| History of pelvic inflammatory disease | 0 (0) | 5 (1.1) | 0.589 |
| Previous pelvic radiation | 1 (0.9) | 6 (1.3) | 1 |

Data are presented as median (interquartile range) or n(%).

Among type of surgery performed in patients with urological injuries, open abdominal surgery was still the most common route of gynecologic surgeries. Total abdominal hysterectomy with bilateral salpingo-oophrorectomy was the most common procedure, causing urological injuries in 69 patients (59%). Other surgeries included: total abdominal hysterectomy in 18 patients (15.4%), followed by adnexal operation in 11 patients (9.4%), radical hysterectomy in 9 patients (7.7%) and interval debulking surgery for ovarian cancer in 3 patients (2.6%). Laparoscopic surgery and vaginal surgery were the minority among the gynecologic surgeries as shown in Table 2.

**Table 2.** Type of surgery performed in patients with urological injuries (n = 117).

| Type of surgery | Number of cases (%) |
|---|---|
| Abdominal surgery | |
| Open | |
| TAH with BSO | 69 (59) |
| TAH | 18 (15.4) |
| Adnexal operation | 11 (9.4) |
| Radical hysterectomy | 9 (7.7) |
| Interval debulking surgery | 3 (2.6) |
| Laparoscopic | |
| Total laparoscopic hysterectomy | 1 (0.9) |
| Lysis adhesion | 1 (0.9) |
| Vaginal surgery | |
| Vaginal hysterectomy | 3 (2.6) |
| V-NOTES hysterectomy | 2 (1.7) |

TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophrorectomy, V-NOTES: vaginal natural orifice transluminal endoscopic surgery hysterectomy

The most common indication for surgery in cases of urological injuries was ovarian cancer for 34 patients (29%), followed by endometriosis, benign ovarian tumor in 30 patients (26%) and uterine leiomyoma in 25 patients (21%). In the urologic injury group, there was a significance in greater blood loss, longer operative time and longer length of hospital stay ($p < 0.001$). However, there were no statistically significant differences regarding the surgical indication between the two groups ($p = 0.576$) as shown in Table 3.

**Table 3.** Risk factors associated with urological injuries.

| Risk factors | Cases (n = 117) | Control (n = 468) | p value |
|---|---|---|---|
| Level of surgeon | | | < 0.001 |
| Staff | 106 (90.6) | 322 (68.8) | |
| Fellow/Resident | 11 (9.4) | 146 (31.2) | |
| Surgical indication | | | 0.576 |
| Malignant; | 57 (48.7) | 212 (45.3) | |
| Ovarian cancer | 34 (29.1) | 85 (18.2) | |
| Cervical cancer | 11 (9.4) | 43 (9.2) | |
| Uterine cancer | 9 (7.7) | 75 (16.0) | |
| Others | 3 (2.6) | 9 (1.9) | |
| Benign; | 60 (51.3) | 256 (54.7) | |
| Uterine leiomyoma | 25 (21.4) | 105 (22.4) | |
| Endometriosis | 15 (12.8) | 64 (13.7) | |
| Ovarian tumor | 15 (12.8) | 60 (12.8) | |
| Others | 5 (4.2) | 27 (5.8) | |
| Pelvic adhesion | | | < 0.001 |
| No | 38 (32.5) | 253 (54.1) | |
| Dense | 70 (59.8) | 161 (34.4) | |
| Filmy | 9 (7.7) | 54 (11.5) | |
| Mass size (cm) | 12 (9, 18) | 10 (8, 15) | 0.038 |
| Estimated blood loss (mL) | 950 (500, 1900) | 300 (150, 600) | < 0.001 |
| Operative time (minutes) | 280 (240, 325) | 195 (154.2, 258) | < 0.001 |
| Length of hospital stay (days) | 12 (9, 16) | 6 (5, 9) | < 0.001 |

Data are presented as median (interquartile range) or n (%)

To identify risk factors associated with urological injuries, we found that there were three significant variables, which included: presence of pelvic adhesion ($p < 0.001$), large tumor size ($p = 0.038$) and level of surgeon ($p < 0.001$). The results of multiple conditional logistic regression are shown in Table 4. The statistically significant risk factors were previous myomectomy (OR 9.25, 95%CI 1.93-44.23), level of surgeon (OR 3.44, 95%CI 1.63-7.24), the presence of dense pelvic adhesion (OR 1.99, 95%CI 1.07-3.7) and large tumor size (OR 1.06, 95%CI 1.01-1.1).

**Table 4.** Multiple conditional logistic regression analysis for risk factors associated with urological injuries.

| Risk factors | Crude OR (95% CI) | Adjusted OR (95%CI) | p value |
|---|---|---|---|
| Age | 0.98 (0.96-1) | 0.98 (0.95-1) | 0.095 |
| Previous pelvic surgery | | | |
| No | 1 | 1 | |
| Cesarean section | 1.35 (0.77-2.4) | 1.34 (0.66-2.72) | 0.414 |
| Myomectomy | 3.8 (1.14-12.7) | 9.25 (1.93-44.23) | 0.005 |
| Adnexal operation | 4.05 (1.43-11.45) | 2.53 (0.6-10.67) | 0.207 |
| Others | 1.22 (0.7-2.11) | 1.39 (0.68-2.84) | 0.371 |
| Level of surgeon | | | |
| Fellow/resident | 1 | 1 | |
| Staff | 5.58 (2.81-11.08) | 3.44 (1.63-7.24) | 0.001 |
| Pelvic adhesion | | | |
| No | 1 | 1 | |
| Dense | 3.45 (2.11-5.62) | 1.99 (1.07-3.7) | 0.03 |
| Filmy | 1.2 (0.54-2.66) | 1.33 (0.52-3.39) | 0.551 |
| Mass size | 1.05 (1.01-1.08) | 1.06 (1.01-1.1) | 0.01 |
| Estimated blood loss | 1.0011 (1.0008-1.0014) | 1.0009 (1.0006-1.0013) | < 0.001 |

OR: odds ratio, CI: confidence interval.

Of the 117 patients with urological injuries, most cases (110 patients, 94%) were detected and repaired during the concurrent operation. Most bladder injuries were corrected by primary repair, while ureteric injury was repaired by end-to-end anastomosis, ureteroneocystostomy and ureteral stent indwelling, respectively (Table 5).

**Table 5.** Multiple conditional logistic regression analysis for risk factors associated with urological injuries.

| Site of injury | Management | Number of cases (%) |
|---|---|---|
| Bladder | Primary repair | 47 (40.2) |
| | Cystostomy | 23 (19.7) |
| | Primary repair with peritoneal flap | 1 (0.8) |
| | Bladder catheterization | 1 (0.8) |
| Ureter | End-to-end anastomosis | 16 (13.7) |
| | Ureteroneocystostomy | 11 (9.4) |
| | Ureteral stent indwelling | 10 (8.6) |
| Bladder and ureter | Primary repair with end-to-end anastomosis | 2 (1.7) |
| | Primary repair with ureteroneocystostomy | 4 (3.4) |
| | Cystostomy with ureteral stent indwelling | 1 (0.8) |
| | Boari flap with ureteroneocystostomy | 1 (0.8) |

Of all the primary repairment, 116 (99.1%) were successful. Only one patient who underwent vaginal hysterectomy had a consequence of complicated vesicovaginal fistula at 1 month after the primary repair; this required a secondary repair. Seven patients (6%) were detected post operation. One of them had a bladder injury, and the other had a ureteric injury (Table 6). The presenting symptoms included: abdominal pain, fever, and urine leakage from the vagina.

**Table 6.** Multiple conditional logistic regression analysis for risk factors associated with urological injuries.

| Site of injury | Intraoperative | Postoperative | Total | p value |
|---|---|---|---|---|
| Bladder | 73 (66.4) | 1 (14.3) | 74 (63.2) | 0.01 |
| Ureter | 30 (27.3) | 6 (85.7) | 36 (30.8) | 0.003 |
| Bladder and ureter | 7 (6.4) | 0 (0) | 7 (6) | 1.000 |

Data are presented as n(%).

# Discussion

Urinary tract injuries have been recognized as a potential complication of gynecologic surgery, with up to 75% of urinary tract injuries being due to gynecologic surgery[1]. The worldwide incidence varies from 0.2% to 1.34%[1-5]. Another study in Thailand reported an incidence of 0.3%[6]. However, the true incidence of urinary tract injures from gynecologic surgery was underestimate, was mostly from a single center, with a small-scale dataset in some centers. From this study, we found that the incidence of overall urologic injuries was 0.66%. This was slightly higher than most previous reports, because this study was conducted at Songklanagarind hospital, which is only university-based hospital in Southern, Thailand, and is involved in resident training programs. Our setting has more complicated benign and malignant gynecological cases referred from other hospitals.

In this study, open pelvic surgery was the majority cause of urological injuries at 94%, especially abdominal hysterectomy, similarly to prior studies[2, 6, 7, 10]. While Desai et al reported the highest incidence in radical hysterectomy[3]. Laparoscopic surgery has gained worldwide popularity since the early 1900s, leading to increasing incidence of ureteral injuries[1, 8, 12]. In contrast, a recent systematic review showed the overall urinary tract injury rate for laparoscopic hysterectomy was 0.73%, with no significant increase in risk[13]. This type of surgery is still the minority in our setting; therefore, the number of urinary tract injuries in this group was few (1.8%). Urinary bladder was the most common site of urological injuries (0.42%), followed by ureteric injury (0.19%) and combined bladder and ureteric injury (0.04%). These findings were similar to previous studies[2, 6, 7, 11].

Regarding the indication for surgery, the most common indication that led to causes of urological injuries was ovarian cancer (29%). However, the gynecological condition was not a significant risk factor ($p = 0.576$) in this study compared to prior studies, which indicated that ovarian neoplasms and endometriosis have been recognized as increasing the risk[8,14]. In this current study, we found that there were three significant variables, including presence of pelvic adhesion, large tumor size and level of surgeon, that were significant risk factors for urologic injury ($p < 0.05$). Presence of pelvic adhesion and large tumor size were the influencing factors, these were also demonstrated in other studies[6, 15]. Surprisingly, in our study we found that the level of the primary surgeon was a contributing factor, which has never been reported in previous studies. It may be from complicated and difficult operations that require attending staff as the primary surgeon and causes damage to the urinary tract. Furthermore, we could not identify some variables, such as previous pelvic surgery, chronic pelvic inflammatory disease or previous irradiation as a significant risk factor when compared to the reports in many other studies[5, 6, 8, 14]. Additionally, in the subgroup analyzed by multiple conditional logistic regression, the data

showed that previous myomectomy was consider a significant risk factor, which has never been reported in prior studies. As a consequence of urologic injuries, this group had a significantly greater blood loss, increased operative time and required a longer length of hospital stay ($p < 0.001$) similar to previous reports[6-8].

Most cases of urological injury (94%) were detected and repaired during the concurrent operation, this led to better outcomes, with a high success rate of up to 99.1% in our series. The majority of the bladder injuries were corrected by primary repair, whereas ureteric injuries were repaired by end-to-end anastomosis. The type of procedure was dependent on site, complexities of the injuries and preference of the urologists. Routine preoperative imaging has not been shown to reduce the incidence of lower urinary tract injuries, although cystourethroscopy should be performed if indicated[16]. Prophylactic urethral stenting was recommended in patients with potential risks, such as a history of previous pelvic surgery or pelvic adhesion. This makes the identification of the ureter easier, so as to minimize the injury[8, 17]. However, the result has not shown a statistically significant decrease in the ureteral injury rate[18], and its cost-effectiveness was lower than anticipated[19, 20].

The strength of this study was the design of its case-control, by matching the same surgical procedure, surgical indication and period, with a high ratio at 1:4 of case-to-control. This method may help to minimize the confounding factors. Our study had a limitation, due to it being a retrospective study; therefore, some detailed information may be incomplete or unrecord in the patient' charts.

The current study provided practical information for early detection of urinary tract injuries in patients who had significant risk factors. Patients with significant risk factors should be identified and evaluated thoroughly prior to surgery. In some cases, the urologists should also be counseled prior to the procedure. Gynecologic surgeons must have a thorough understanding of pelvic anatomy. Furthermore, the proper surgical technique should be used. During the operation, urinary tract organs, particularly the ureters, should be identified. If urinary tract injuries occur, they will be detected during the operation and prompt management. However, despite these efforts, the risk of unintended damage to the urinary organs remains. Thus, early recognition and prompt management are critical to reduce morbidity. This study provided evidence in terms of incidence, risk factors, management of urinary tract injuries and surgical outcomes. Counseling and informed consent are fundamental before planning surgery, particularly for patients who are at high risk.

## Conclusion

The incidence of urological injury during gynecologic surgery at Songklanagarind hospital was 0.66%, over a 15-year period. Bladder injuries were the most common type of urologic injuries. Previous myomectomy, level of surgeon, the presence of dense pelvic adhesion, and large tumor size were significant risk factors. Eventually, most injuries were detected, and promptly repaired in concurrent procedures, by skillful urologists with successful outcomes.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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## OBSTETRICS

# Uterocervical Angle Measurement for Prediction Spontaneous Preterm Birth in Twin Pregnancy

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### ABSTRACT

**Objectives:** This study's objective determined the predictive value of the uterocervical angle in predicting preterm birth in twin pregnant women at 16-23$^{+6}$ weeks of gestation.

**Materials and Methods:** A diagnostic study was conducted in twin pregnant women at 16-23$^{+6}$ weeks of gestation who had prenatal care at the King Chulalongkorn Memorial Hospital between March 2019 and February 2020. Uterocervical angle and cervical length were assessed at 16-23$^{+6}$ weeks of gestation. Optimal cut-off for the uterocervical angle was obtained to calculate the predictive values for preterm birth.

**Results:** A total of 84 pregnant women were included in this study. Thirty-eight cases (47.5%) developed preterm birth. Women who delivered < 37 weeks had significantly higher uterocervical angles compared to those who delivered ≥ 37 weeks (109.32 degrees vs. 96.41 degrees, p = 0.016). The optimal cut-off of the uterocervical angle was 102 degrees. Sensitivity specificity, positive predictive value, and negative predictive value were 65.8%, 61.9%, 61.9%, and 68.4%, respectively.

**Conclusion:** The uterocervical angle was an easy technique that could be one of the screening tools to predict preterm birth among twin pregnant women who had an angle equal to or greater than 102$^{o}$, with a sensitivity, positive predictive value, and a negative predictive value of more than 60%.

**Keywords:** cervical length, preterm birth, second trimester, uterocervical angle, twin pregnancy.

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# *การทำนายภาวะคลอดก่อนกำหนดโดยวัดมุมระหว่างมดลูกส่วนล่างและปากมดลูก โดยการตรวจอัลตราซาวด์ทางช่องคลอดในสตรีตั้งครรภ์แฝด*

***ปาณิสรา นิยมแย้ม, ธีระภัทร เจริญวิทย์, บุญชัย เอื้อไพโรจน์กิจ***

## *บทคัดย่อ*

***วัตถุประสงค์:*** *วัตถุประสงค์หลักเพื่อหาค่าคาดทำนาย (Predictive value) จากการวัดมุมระหว่างมดลูกส่วนล่างและปากมดลูก โดยการตรวจอัลตราซาวด์ทางช่องคลอดในสตรีตั้งครรภ์แฝดที่มีอายุครรภ์ 16 - $23^{+6}$ สัปดาห์ ต่อการเกิดภาวะคลอดก่อนกำหนด วัตถุประสงค์รองคือ หาค่าคาดทำนาย (Predictive value) จากการวัดความยาวปากมดลูก โดยการตรวจอัลตราซาวด์ทางช่องคลอดในสตรีตั้งครรภ์แฝดที่มีอายุครรภ์ 16 - $23^{+6}$ สัปดาห์ ต่อการเกิดภาวะคลอดก่อนกำหนด และหาค่าคาดทำนาย (Predictive value) จากการวัดมุมระหว่างมดลูกส่วนล่างและปากมดลูก โดยการตรวจอัลตราซาวด์ทางช่องคลอดในสตรีตั้งครรภ์แฝดที่มีอายุครรภ์ 16 - $23^{+6}$ สัปดาห์ ต่อการเกิดภาวะเจ็บครรภ์คลอดก่อนกำหนด*

***วัสดุและวิธีการ:*** *รูปแบบการศึกษาเป็นการศึกษาแบบ Diagnostic study ทำการศึกษาในหญิงตั้งครรภ์แฝดที่มีอายุครรภ์ระหว่าง 16 – 23+6 สัปดาห์ ที่มารับการตรวจฝากครรภ์ที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนมีนาคม พ.ศ. 2562 ถึงธันวาคม พ.ศ.2563 โดยการตรวจคลื่นเสียงความถี่สูงทางช่องคลอดเพื่อวัดมุมระหว่างมดลูกส่วนล่างและปากมดลูก และวัดความยาวปากมดลูกที่ช่วงอายุครรภ์ระหว่าง 16 - $23^{+6}$ สัปดาห์ ติดตามหญิงตั้งครรภ์จนคลอด เก็บข้อมูลการคลอด นำค่าการวัดมาหาค่าที่เหมาะสมในการทำนายภาวะคลอดก่อนกำหนดและเพื่อคำนวณหาค่าพยากรณ์การเกิดภาวะคลอดก่อนกำหนด*

***ผลการศึกษา:*** *หญิงตั้งครรภ์แฝดที่นำมาวิเคราะห์ทั้งหมด 80 ราย พบการคลอดก่อนกำหนด 38 ราย (47.5%) เมื่อเปรียบเทียบกับหญิงตั้งครรภ์แฝดที่คลอดครบกำหนด พบว่าหญิงตั้งครรภ์ที่คลอดก่อนกำหนดมีค่าของมุมระหว่างมดลูกส่วนล่างและปากมดลูกมากกว่าอย่างมีนัยสำคัญทางสถิติ (109.32 ± 19.12 องศา กับ 96.47 ± 26.57 องศา, P=0.016) และค่ามุมระหว่างมดลูกส่วนล่างและปากมดลูกที่เหมาะสมในการทำนายภาวะคลอดก่อนกำหนด เท่ากับ 102 องศา เมื่อใช้ค่ามุมระหว่างมดลูกส่วนล่างและปากมดลูกในการทำนายการเกิดภาวะคลอดก่อนกำหนดพบค่าความไว ค่าความจำเพาะ ค่าทำนายผลบวก และค่าทำนายผลลบ เท่ากับร้อยละ 65.8, 61.9, 61.9, และ 68.4 ตามลำดับ*

***สรุป:*** *การวัดมุมระหว่างมดลูกส่วนล่างและปากมดลูกโดยการตรวจคลื่นเสียงความถี่สูงทางช่องคลอดเป็นเทคนิคหนึ่งที่สามารถนำมาใช้คัดกรองหญิงตั้งครรภ์แฝดที่มีความเสี่ยงการเกิดภาวะคลอดก่อนกำหนดได้ โดยที่มุมระหว่างมดลูกส่วนล่างและปากมดลูกมากกว่าหรือเท่ากับ 102 องศาจะมีค่าความไว ค่าความจำเพาะ ค่าทำนายผลบวกและค่าทำนายผลลบที่มากกว่า 60%*

***คำสำคัญ:*** *ความยาวของปากมดลูก, คลอดก่อนกำหนด, การตั้งครรภ์ในไตรมาสที่สอง, มุมระหว่างมดลูกส่วนล่างและปากมดลูก, ครรภ์แฝด*

## Introduction

The incidence of twin pregnancy has rapidly increased for many years due to advanced maternal age and increased use of assisted reproductive technology[1]. Twin pregnancy has a 50% risk of having a preterm birth, of which 10% occur before 32 weeks, and are related to a higher risk of neonatal death and long-term complications, especially neurodevelopmental disability[2-4]. Over the past few years, the rate of preterm births in twin gestation at the King Chulalongkorn Memorial Hospital, Bangkok, was 40.2%[5].

Previous studies have investigated screening tests for preterm births in twin gestation, including ultrasound to measure the cervical length and the fetal fibronectin test. Unfortunately, these screening tests have poor diagnostic performance[6-11]. It has been shown that during pregnancy, there are cervical changes due to the weight of the fetus, placenta, and amniotic fluid, which press down on the lower part of the uterus and cervix. These changes result in subsequent alterations of the cervical length and the angle between the lower uterine segment and the cervix[12-14]. It has been found that a pessary could narrow the uterocervical angle and subsequently prevent preterm birth[15,16]. According to Dziadosz et al[17], a wide uterocervical angle increases the risk for preterm birth. Thus, investigations of the uterocervical angle measurement may be helpful in predicting preterm birth among twin pregnant women.

This study investigated the performance of uterocervical angle at 16-23+6 weeks of gestation in predicting preterm birth in twin gestation.

## Materials and Methods

This study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, from March 2019 - February 2020. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all the patients before any procedures were done.

Twin pregnant women with a gestational age of 16-23$^{+6}$ weeks were invited to participate in this study. The exclusion criteria were monochorion-monoamnion pregnancy, complications specific to monochorionicity (i.e., twin-twin transfusion syndrome (TTTS), and twin anemia-polycythemia sequence), a complication from twin pregnancy (i.e., fetal demise in one twin, and selective reduction of one twin), cervical cerclage, use of vaginal Arabin pessary, placenta previa, lethal fetal anomalies, and medically indicated preterm birth.

The sample size calculation was based on the sensitivity of the uterocervical angle measurement used to improve the prediction of preterm birth in twin gestation by Knight et al[18] (sensitivity = 0.8). At the King Chulalongkorn Memorial Hospital, the incidence of preterm birth in twin pregnancies was 40.2%. Based on this calculation, the number of participants needed was 70. When a 20% attrition rate of the follow-up participants was included in the calculation, the total sample size was increased to 84 pregnant women.

The primary outcome was to investigate the clinical performance of uterocervical angle in predicting preterm birth at a gestational age of 16-23$^{+6}$ weeks in twin pregnancy. The secondary outcome was to determine the clinical performance of the cervical length in predicting preterm birth. The cervical length and uterocervical angle measurements were performed by a single doctor (maternal-fetal medicine fellow monitored by maternal-fetal medicine staff) using the ultrasound machine GE Voluson E10 and IC5-9-D Endovaginal transducer (4-9 MHz). The cervical length and uterocervical angle were measured by transvaginal ultrasound as per the standard technique[19]. Briefly, the cervix should be measured along its longitudinal axis. The cervix should involve approximately 50–75% of the image. Excessive pressure on the cervix by the transvaginal probe should be avoided, as the cervix artificially appears to be longer, and the presence of a funnel will be obscured. The cervical length is the distance from the internal os to the external os. Three cervical length measurements were assessed, and the shortest value was used in the analysis[20].

The uterocervical angle is between the lower uterine segment and the cervical canal[17]. The first line

is traced from the internal os of the cervix to the external os of the cervix. The second line is then drawn straight along the lower uterine segment. The angle between the two lines is then measured using a program in the ultrasound machine, as shown in Fig. 1. Three measurements were obtained, and the average value was used for analysis. The varying values were typically no more than 10% for all measurements.

***Statistical analysis***

The data were analyzed with the SPSS software version 22.0 for Windows and presented as the mean, standard deviation, median, interquartile range, sensitivity, specificity, positive predictive value, and negative predictive value. Kappa coefficient was performed. The optimal cut-off values for the uterocervical angle were calculated using the receiver operator characteristic curve. We used a chi-square test, Fisher's exact test for categorical variables, and an independent t-test for continuous variables. Mann-Whitney U test was used for nonparametric variables. A p-value of < 0.05 was considered to be statistically significant.

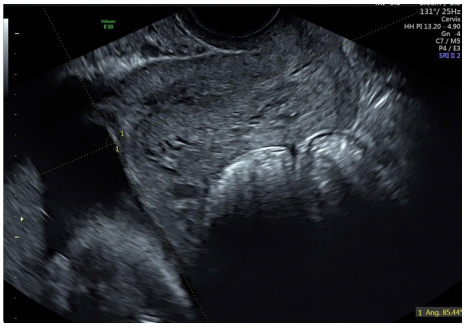

**Fig. 1.** The uterocervical angle (UCA) is between the lower uterine segment and the cervical canal. The UCA is 85.44 degrees.

# Results

A total of 84 twin pregnant women were enrolled in this study. Four cases were excluded: one case had the fetal demise of one twin, one case had TTTS, one case had severe preeclampsia, one case was lost to follow-up. This left 80 twin pregnant women for analysis. Thirty-eight cases (47.5%) developed preterm birth. The cervical length and uterocervical angle were measured three times, and the kappa coefficient for intraobserver variability was 0.968 and 0.987, respectively. There were no statistically significant differences between the characteristics of term and preterm births in twin gestation, including age, the number of pregnancies, use of assisted reproductive technology, history of preterm birth, body mass index, and underlying disease (hypertension and diabetes) (Table 1).

Gestational age at the time of the transvaginal ultrasound for the cervical length and uterocervical angle assessment showed that the cervical length was not statistically significant in the two groups (Table 2). The uterocervical angle of the preterm group was significantly more expansive than the term group (109.32 o vs. 96.41 o, p = 0.016)

The receiver operator characteristic curve was performed to evaluate delivery prediction before 37 weeks. The area under the curve for the uterocervical angle was 0.653 (p = 0.019, 95% confidence interval 0.529-0.776) (Fig. 2.). The optimal performance of the uterocervical angle was found at 102°, which had a sensitivity of 65.8%, a specificity of 61.9%, a positive predictive value of 61.9%, and a negative predictive value of 68.4%.

**Table 1.** Demographic characteristics of the twin pregnant participants in the study.

| Characteristic | Gestational age ≥ 37 weeks (n = 42) | Gestational age < 37 weeks (n = 38) | p value |
|---|---|---|---|
| Maternal age (years) | 32.79 ± 4.16 | 32.47 ± 4.34 | 0.744§ |
| Nulliparous | 32 (76.19%) | 26 (68.42%) | 0.437† |
| ART | 21 (50.00%) | 18 (47.36%) | 0.814† |
| Chorionicity | | | 0.026† |
| - MCDA | 9 (21.42%) | 17 (44.74%) | |
| - DCDA | 33 (78.58%) | 21 (55.26%) | |
| Prior spontaneous preterm birth | 0 | 1 (2.63%) | 0.475‡ |
| BMI at prepregnancy (kg/m$^2$) | 22.54 ± 4.04 | 23.17 ± 4.17 | 0.492§ |
| Hypertensive disorder | 5 (11.90%) | 6 (15.79%) | 0.614† |
| Diabetes/gestational diabetes | 5 (11.90%) | 5 (13.15%) | 0.866† |
| GA at delivery (weeks) | 37.02 ± 0.98 | 34.34 ± 3.12 | 0.001† |

Data are presented as n (%) or mean ± standard deviation.
† chi-square test, ‡ Fisher's exact test, § Student's t-test
ART: assisted reproductive technology, MCDA: monochorionic diamniotic, DCDA: dichorionic diamniotic, BMI: body mass index, GA: gestational age

**Table 2.** Characteristics of uterocervical angle and cervical length in twin pregnancy.

| Characteristic | Birth ≥ 37 weeks (n = 42) | Birth < 37 weeks (n = 38) | p value |
|---|---|---|---|
| GA at ultrasound screen (weeks) | 19.85 (17.14 - 23.85) | 20.42 (17.14 - 23.85) | 0.904§ |
| UCA (degree) | 96.41 ± 26.57 | 109.32 ± 19.12 | 0.016* |
| CL (mm) | 38.98 ± 5.13 | 39.67 ± 6.19 | 0.587* |

Data are presented as mean ± standard deviation or median (interquartile range)
§ Mann-Whitney U Test, * Student's t-test
GA: gestational age, UCA: uterocervical angle, CL: cervical length

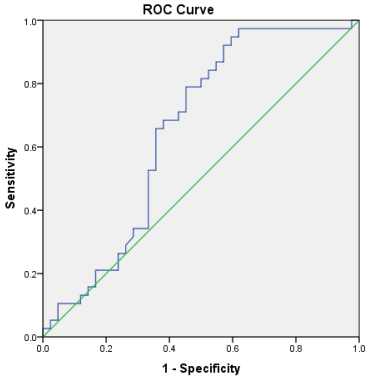


**Fig. 2.** Receiver operating characteristic (ROC) curves of the uterocervical angle are used to predict spontaneous preterm birth in twin pregnancy.

## Discussion

The preterm birth rate for twin pregnancies was approximately 50%, resulting in increased perinatal morbidity and mortality[2-4]. Recent studies have investigated the mechanism of the cervical changes during pregnancy, which found that the physical body changes of the pregnant women affected the cervical length and the uterocervical angle[12-14]. In particular, they found that pessary use caused the uterocervical angle to narrow down, which increased the effectiveness of preventing preterm birth[15,16]. According to The American College of Obstetricians and Gynecologists guidelines, there is currently no recommendation for cervical length screening for all twin pregnant women with no history of preterm delivery[22].

The cervical length measurement investigation in this study found that there was no significant difference between the 2 groups. These results were similar to Hester et al[23] who measured the cervical length at 16-20 weeks of gestation to predict preterm birth in twin pregnancies. They found that cervical length in preterm birth < 34 weeks was not statistically significant (37.2 vs. 40.7, p = 0.66). The cervical length was a poor predictor for preterm birth in twin pregnancy. Knight et al[18] compared the uterocervical angle and cervical length to predict preterm birth between the gestational ages of < 28 weeks and < 32 weeks in twin pregnant women. They found that a uterocervical angle > 110 o had a sensitivity of 80%, specificity of 82%, and a negative predictive value of 97.1% to predict preterm birth at gestational age before 32 weeks. This result was similar to the prediction of preterm at gestational < 28 weeks when the uterocervical angle was > 114o; the sensitivity was 80%, specificity was 84%, and the negative predictive value was 99%. When the two studies were compared, it was found that the uterocervical angle widened significantly, which may affect the preterm birth rate. Our results had lower sensitivity, specificity, and negative predictive value than the studies mentioned above. This may be due to the study's primary outcome that used uterocervical angle and cervical length to predict preterm birth < 37 weeks. The strength of this study was that it was a diagnostic study that a single operator conducted. However, the limitation of this study was its small sample size. Additional studies with a larger sample size may detect other factors significantly associated with predicting preterm birth.

## Conclusion

In conclusion, the uterocervical angle was an easy technique that could be one of the screening tools used to predict preterm birth among twin pregnant women with an angle equal to or greater than 102°. This technique had a sensitivity of 65.8%, a positive predictive value of 61.9%, and a negative predictive value of 68.42%.


## Acknowledgement

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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