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EDITORIAL

This sixth issue of Thai Journal of Obstetrics and Gynaecology 2022 contains many interesting articles. One special article is “Cervical Cancer Screening in Elderly Women”. This article reviews current cervical cancer screening recommendations and benefits versus risks of cervical cancer screening in women older than 65 years.

Editor in Chief and managing staff of the Thai Journal of Obstetrics and Gynecology already attended an online meeting "System development and quality improvement of Thai journals in the Scopus database (TCI-TSRI-Scopus Collaboration Project "on October 5, 2022, 10:00 a.m.–11:00 a.m.. Editor in Chief and the journal working group in the project, which used the Editorial Manager (EM) system, totaling 15 journals (23 people) from 42 journals in the project attended this meeting. The purpose was to share the experience of using the system. The quality of Thai Journal of Obstetrics and Gynaecology is continuously rising.

For the coming New Year 2023, we would like to extend our warmest wishes to RTCOG members, editorial board, reviewers, authors and families. We thank to all the authors, readers, reviewers, and editors for your contributions to TJOG this past year and look forward to receiving your valuable contributions in 2023.

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

Thai Journal of Obstetrics and Gynaecology
November 2022, Vol. 30, No. 6, pp. 370-375.

SPECIAL ARTICLE

Cervical Cancer Screening in Elderly Women

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ABSTRACT

Cervical cancer (CC) is the one of the leading causes of cancer death among women worldwide. Globally, with the current projections for increases in life expectancy, the prevalence of CC in elderly women is expected to rise, increasing the desirability of CC screening to detect the disease at an earlier stage in this group. However, making the decision to screen for CC in elderly women is often difficult and complex. The decision needs to be made using the best available evidence and a personalized assessment that integrates factors unique to elderly women with the aim to weigh the risks and benefits for each woman. The recent 2020 United States guideline update from the American Cancer Society recommends against cervical screening beyond age 65 in women who have had adequate negative screening results. Despite the evidence cited for this recommendation, implementation in a clinical practice guideline can be challenging, with resistance from elderly women and clinicians. Following is a brief review of current knowledge concerning the CC screening in elderly women. We also review the benefits and risks of CC screening in women older than 65 years.

Keywords: cervical cancer, screening, elderly women, guideline.

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Introduction

Cervical cancer (CC) is one of the most burdensome cancers worldwide and the fourth most common cancer among Thai women, ranking after breast, lung, and liver and intrahepatic bile duct cancers[1,2]. Persistent infection with human papillomavirus (HPV), especially the high-risk type, is the major risk factor for CC[2]. The age distribution of CC incidence is bimodal, with the first peak at around 40 years of age with a secondary peak at around 60 years of age[3]. While scientific evidence supports CC screening programs such as cytology alone (liquid-based or conventional), primary HPV testing, or co-testing (HPV testing and cytology) for early detection and treatment of CC, thus reducing CC incidence, mortality and treatment-related morbidity, there are few studies which have focused on the benefits of such programs in elderly women[4].

With the ever-increasing age of the world's population, the number of cancers in the elderly will proportionally increase[3, 5]. In the United States (USA), the American Cancer Society (ACS) (2018) reported that more than 15% of CC patients were diagnosed in women aged > 65 years[6]. Recently, data from the Massachusetts Cancer Registry reported that nearly one-in-four (23.6%) women with CC are diagnosed at > 65 years[7]. Other studies have reported that elderly women were more frequently diagnosed with advanced stage CC and oncological outcomes worsened with increasing age and stage of diagnosis[3, 8]. A previous population-based study from Japan reported that relative 5-year overall survival for CC patients decreased with age (88.6% in patients < 30 years, 78.1% in 30-54 years, 67.7% in 55-64 years and 54.4% in 65+ years)[9]. There is also some evidence that older age at diagnosis is related with advanced stage of CC, probably because of the late presentation among patients[9, 10].

Several studies have reported that elderly women often do not get CC screening tests[11, 12]. There are several possible explanations for these lower rates of CC screening in older women[13]. First, many CC screening guidelines recommend that women at low risk can stop screening at age 65[4, 14, 15]. Second, life expectancy among elderly women decreases with increasing age, and the utility of CC screening decreases proportionately. And, as such, many elderly women and clinicians may be unwilling to continue with CC screening as women age into their seventh decade and more. Third, in elderly women, there is a lack of knowledge on the prevalence and natural history of HPV, and HPV-related cervical dysplasia/cancer. Finally, regarding anatomical and hormonal changes, and musculoskeletal disorders in elderly women, there may be perceptions that these changes such as vaginal atrophy may cause screening examinations to be painful and burdensome.

As reviewed below, determining the optimal CC screening regime for elderly women is considerably complex. To better understand this topic, this article will briefly review the current knowledge on CC screening, especially in elderly women. We also review the benefits and risks of CC screening in women older than 65 years.

Current cervical cancer screening recommendations

CC screening guidelines differ among countries with established national screening programs and even professional organizations (Table 1.)[4, 14, 15]. These differences include type of screening test, screening intervals, and the age at which women should start/stop having CC screening. Most of the disagreements stem from the type of screening test that each country/professional organization uses to formulate their recommendations, their interpretations of the evidence, and considerations about the balance between benefits, costs, and risks. The guidelines vary in the ages at which they recommend beginning (20-25 years) and ending (65-70 years) screening.

Table 1. Comparison of selected cervical cancer screening guidelines.

	ACS[14]	ACS[14]	RTCOG[4]	Australia[15]	Japan[15]
Published	- 2012	- 2020	- 2021	- 2017	- 2010
Age start	- 21 years	- 25 years	- 25 years with a history of sexual intercourse - 30 years without a history of sexual intercourse	- 25 years	- 20 years
Age stop	- 65 years	- 65 years	- 65 years	- 70 years	- No end date included
Test and interval	- 21-29 years; every 3 years with cytology - 30-65 years; every 3 years with cytology or co-testing - Primary HPV testing alone not recommended	- Every 5 years with primary HPV testing alone or co-testing or - Every 3 years with cytology	- Every 2 years with cytology or - Every 5 years with co-testing	- Every 5 years with primary HPV testing alone or co-testing	- Every 2 years with cytology
Post-hysterectomy	- Not recommended for women with no history of serious precancer of cervix or more lesions.	- Not recommended for women with no history of CIN2 or more lesions.	- Omit screening if hysterectomy was done for benign condition.	- Omit screening if no evidence of cervical pathology was detected on the hysterectomy specimen.	- Not mentioned.

ACS: American Cancer Society, RTCOG: The Royal Thai College of Obstetricians and Gynaecologists, CIN: cervical intraepithelial neoplasia

The 2020 guideline update from the ACS recommends that CC screening should start at age 25 years and then the woman should undergo primary HPV testing every 5 years until age 65 years. In a setting in which primary HPV testing is not available, then women aged 25-65 years should be screened with co-testing every 5 years or by cervical cytology alone every 3 years. This guideline recommends that women aged > 65 years who have no history of cervical intraepithelial neoplasia (CIN) II or more severe lesions in the past 25 years, and who have documented adequate negative prior screening results in the previous 10 years, discontinue all CC screening[14].

Adequate negative prior screening is described as 2 sequential negative primary HPV testing results, or 2 sequential negative co-testing results, or 3 sequential negative cytology results in the past 10 years, with the most recent test occurring within the past 3-5 years, depending on the screening test used. This guideline still suggests that women aged > 65 years

without conditions restricting life expectancy for whom adequate documentation of prior screening is not available should be screened until the criteria for screening cessation are met. CC screening may be ceased in women of any age with restricted life expectancy[14].

A strong evidence base has been compiled in recent years from the integration of good randomized controlled studies and population-based observational studies to inform recommendations for both type of CC screening test and screening interval time, although there are still gaps concerning the specific age at which testing should be started or the age and conditions under which women can safely exit CC screening. And due to this quite serious knowledge gap, recommendations concerning CC screening guidelines in these areas are force to depend on mathematical model studies and expert opinion[16].

Benefits and risks of cervical cancer screening in women older than 65 years

The benefits and risks of CC screening in women aged > 65 years are less well established and require further study before firm guidelines. Many of the physiological changes in older women are associated with low levels of estrogen, which results in narrowing of the cervical os and a reduction in the thickness of the cervical epithelium and stromal vascularity, making the cervix more difficult to expose, and thus the transformation zone where CCs are most likely to arise, making it more difficult to obtain an adequate cervical cytology sample and tissue sample, thus lowering the chance of both adequate cervical smears and a successful morphologic diagnosis by cytology and histopathology[17]. Older women have a higher false positive rate from cervical cytology, increasing the risk of further unnecessary investigations (such as repeat cytology, colposcopy, or biopsy) and overtreatment (such as conization). They can also experience pain or distress during or after CC screening[16-19]. Many mathematical model studies have concentrated on the harms of CC screening in women aged > 65 years caused by increased numbers of unnecessary investigations and overtreatments rather than the harms caused by missed CC cases, and such harms and the costs associated with unnecessary investigations and treatments of missed CC cases must also be considered[18]. There are also a lack of qualitative data examining older women's perceptions of the benefits and risks of CC screening, a critical omission in the consideration of the balance of benefits and risks of this procedure[16].

Women who have had a hysterectomy are no longer at risk of CC. Data from five nationwide registers in Denmark reported a high prevalence of hysterectomy in estimating population-based rates of CC at older women[20]. Failure to remove these elderly women who have had a hysterectomy from the population at risk leads to an underestimating of CC incidence rates in older women[18-19]. For example, in the USA from 2000 to 2009, the hysterectomy adjusted incidence rate of CC was 18.6 per 100,000, nearly 60% higher than the unadjusted rate of 11.7 per 100,000[21]. Therefore, some data behind the guidelines that recommend against CC screening in women aged > 65 years might underestimate their CC risk.

Again, the proper age at which we can safely say a woman has had adequate testing to safely discontinue further CC screening is still undecided. One population-based study from Kaiser Permanente Northern California reported that 75% of the women who were diagnosed with CC after age 65 years had not had adequate negative screening prior to the diagnosis[22]. A recent national cohort study from Denmark also reported that 80% of CC women who were diagnosed at age 60 years and older had insufficient screening including never screened. The same study also found that sufficiently screened women were significantly less likely to be diagnosed with advanced stage CC compared to never-screened women. Insufficiently screened women were more likely to be diagnosed with advanced stage CC compared to sufficiently screened women, but the difference was not significant[23]. A study by Yost and Hoekstra found that half of the women who developed CC after age 65 had had adequate screening prior to being diagnosed[24]. Interestingly, one population-based study from England and Wales found that the protective strength of previous negative

screening results for women from CC diminished with time; there were twice as many CC cases which had stopped screening at 65 years old as those at 75 years old[25]. These data suggest that we should consider extending the age of termination of CC screening even in women with a history of adequate negative prior screening.

Another important point of concern is the durability of protection in women aged > 65 years with adequate negative prior screening based on the role of HPV reactivation after latency in the cervix, as well as the risk conferred by newly acquired HPV infections from a new sexual partner. A recent study reported that the rate of new high-risk HPV detection among women aged 30-60 years was 5.0 per 1,000 woman-months. Reporting a new sexual partner was associated with higher HPV detection rates (adjusted hazard ratio, 8.1), but accounted for only 19.4% of all new detections[26]. Based on these findings, we can infer that the most of new HPV infections are probably reactivation of a prior HPV infection. However, as life expectancy increases around the world, many women aged > 65 years are still healthy and have an active sex life, and some of them will have newly acquired HPV infection. One large study from China reported that the risk of high-risk HPV infection in women aged 40 years to menopause is relatively low, but the infection rate increases after 65 years[27]. Moreover, several studies have found that primary HPV testing, whether clinician-collected or self-collected, is more sensitive for detecting precancerous and cancerous cervical lesions than cytology, especially in older women[28-30]. Therefore, women who have a history of multiple sexual partners and an active sex life after 65 years should continue routine CC screening after age 65 years, and use primary HPV testing as the primary screening test.

Conclusion

Decisions about CC screening in elderly women are often difficult, complex, and challenging. Despite the 2020 guideline update from the ACS recommending against CC screening beyond age 65 in women who have had adequate negative screening, nearly one-fourth of women diagnosed with CC are over 65 years of age. As life expectancy increases, older women are an increasingly healthy population. Therefore, the decision regarding when to stop CC screening should not be based on age and previous CC screening history alone. The decision requires a personalized assessment of health status, comorbidities, life expectancy, and cancer risk. It is important to consider the benefits and risks of continued CC screening. Primary HPV testing does seem to be a good method for CC screening in elderly women.

Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Association between Gestational Weight Gain and Small for Gestational Age in Underweight Pregnant Women

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ABSTRACT

Objectives: To compare the rate of small-for-gestational age (SGA), low birth weight (LBW), and other pregnancy outcomes between underweight pregnant women who had adequate and inadequate gestational weight gain (GWG).

Materials and Methods: A total of 300 singleton, uncomplicated, underweight pregnant women were included in a retrospective cohort study. Study group consisted of 100 women who had inadequate GWG and another 200 women who had adequate GWG were in comparison group. Data were retrieved from medical records, including baseline and obstetric characteristics, trimester-specific and total weight gain, delivery data, and pregnancy outcomes. Rate of SGA and other pregnancy outcomes were compared between the 2 groups.

Results: Both groups were comparable in terms of age, BMI, and parity. Compared with women with adequate GWG, those with inadequate GWG had significantly lower weight gain in every trimester. Women with inadequate GWG were significantly more common to have preterm delivery (11% vs. 2%, p = 0.001), LBW (29% vs. 6%, p < 0.001), and SGA (18% vs. 6.5%, p = 0.002). Logistic regression analysis showed that 2nd trimester weight gain ≤ 7 kg was the only independent associated factor for SGA (adjusted odds ratio (OR) 9.92, 95% confidence interval (CI) 2.06-47.68, p = 0.004). On the other hand, inadequate GWG was the only independent associated factor for LBW (adjusted OR 5.82, 95%CI 2.11-16.0, p = 0.001).

Conclusion: Underweight pregnant women who had inadequate GWG significantly increased risk of preterm delivery, LBW, and SGA. Second trimester weight gain ≤ 7 kg was independently associated with SGA and inadequate GWG was independently associated with LBW.

Keywords: underweight, gestational weight gain, small for gestational age, low birth weight.

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ความสัมพันธ์ระหว่างน้ำหนักตัวที่เพิ่มขึ้นขณะตั้งครรภ์กับการคลอดทารกน้ำหนักแรกเกิดน้อยกว่าอายุครรภ์ ในมารดาที่น้ำหนักต่ำกว่าเกณฑ์

ณัฐพร วลีธรชีพสวัสดิ์, บูรยา พัฒนจินดากุล, ดิฐกานต์ บริบูรณ์หิรัญสาร

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการเกิดทารกที่มีนำหนักน้อยกว่าอายุครรภ์ (SGA) ทารกที่มีน้ำหนักน้อยกว่า 2,500 กรัม (LBW) และผลของการตั้งครรภ์ ระหว่างหญิงตั้งครรภ์ที่มีน้ำหนักตัวก่อนตั้งครรภ์ต่ำกว่าเกณฑ์ ที่มีน้ำหนักเพิ่มขึ้นระหว่างตั้งครรภ์ต่ำกว่าเกณฑ์และตามเกณฑ์*

วัสดุและวิธีการ: *ทำการศึกษาแบบ retrospective cohort study ในหญิงตั้งครรภ์เดี่ยวที่มีน้ำหนักตัวก่อนตั้งครรภ์ต่ำกว่าเกณฑ์ และไม่มีภาวะแทรกซ้อนระหว่างตั้งครรภ์ จำนวน 300 คน โดยแบ่งเป็นกลุ่มศึกษาคือหญิงตั้งครรภ์ที่มีการเพิ่มขึ้นของน้ำหนักตัวระหว่างตั้งครรภ์ต่ำกว่าเกณฑ์ (< 12.5 กิโลกรัม) จำนวน 100 คน และกลุ่มเปรียบเทียบคือหญิงตั้งครรภ์ที่มีการเพิ่มขึ้นของน้ำหนักตัวระหว่างตั้งครรภ์ตามเกณฑ์ (12.5-18 กิโลกรัม) จำนวน 200 คน ทำการสืบค้นข้อมูลจากเวชระเบียน ได้แก่ ข้อมูลพื้นฐานทั่วไป ข้อมูลทางสูติศาสตร์ การฝากครรภ์ น้ำหนักตัวระหว่างการตั้งครรภ์ การคลอด และผลลัพธ์ของการตั้งครรภ์ทั้งในส่วนของมารดาและทารก ทำการเปรียบเทียบอัตราการเกิด SGA LBW และผลของการตั้งครรภ์ ระหว่าง 2 กลุ่ม*

ผลการศึกษา: *ทั้ง 2 กลุ่มไม่แตกต่างกันในเรื่องของ อายุ ดัชนีมวลกาย และจำนวนครั้งของการคลอด กลุ่มศึกษามีการเพิ่มขึ้นของน้ำหนักตัวระหว่างตั้งครรภ์และในแต่ละไตรมาสน้อยกว่าอย่างมีนัยสำคัญทางสถิติ กลุ่มศึกษามีอัตราการคลอดก่อนกำหนด ทารกที่น้ำหนักตัวน้อยกว่าอายุครรภ์ LBW และ SGA สูงกว่ากลุ่มเปรียบเทียบอย่างมีนัยสำคัญทางสถิติ (11% และ 2%, p = 0.001; 29% และ 6%, p < 0.001; 18% และ 6.5%, p = 0.002; ตามลำดับ) การวิเคราะห์แบบ Logistic regression analysis พบว่าปัจจัยเสี่ยงต่อการเกิด SGA ได้แก่ การเพิ่มขึ้นของน้ำหนักตัวมารดาในช่วงไตรมาสที่สองไม่เกิน 7 กิโลกรัม (adjusted odds ratio (OR) 9.92, 95% confidence interval (CI) 2.06-47.68, p = 0.004) และปัจจัยเสี่ยงต่อการเกิด LBW ได้แก่ การเพิ่มขึ้นของน้ำหนักตัวระหว่างการตั้งครรภ์ที่ต่ำกว่าเกณฑ์ (adjusted OR 5.82, 95%CI 2.11-16.0, p = 0.001)*

สรุป: *ในหญิงที่มีน้ำหนักตัวก่อนตั้งครรภ์ต่ำกว่าเกณฑ์ที่มีน้ำหนักเพิ่มขึ้นระหว่างการตั้งครรภ์ต่ำกว่าเกณฑ์ เพิ่มความเสี่ยงต่อการเกิด ทารกคลอดก่อนกำหนด LBW และ SGA การเพิ่มขึ้นของน้ำหนักตัวในช่วงไตรมาสที่สองไม่เกิน 7 กิโลกรัม เป็นปัจจัยเสี่ยงที่สำคัญต่อการเกิด SGA ส่วนการมีน้ำหนักเพิ่มขึ้นระหว่างการตั้งครรภ์ต่ำกว่าเกณฑ์ เป็นปัจจัยเสี่ยงที่สำคัญต่อการเกิด LBW*

คำสำคัญ: *น้ำหนักตัวก่อนตั้งครรภ์ต่ำกว่าเกณฑ์ การเพิ่มขึ้นของน้ำหนักตัวระหว่างตั้งครรภ์ ทารกที่น้ำหนักน้อยกว่าอายุครรภ์ ทารกแรกเกิดน้ำหนักน้อย*

Introduction

Maternal overweight and obesity have been associated with various pregnancy complications such as gestational diabetes, preeclampsia, large for gestational age (LGA) infants, macrosomia, cesarean delivery, postpartum hemorrhage, etc[1, 2]. On the other hand, underweight pregnant women were also at higher risk for some other complications, including low birth weight (LBW), small for gestational age (SGA), and preterm birth, as reported from many previous studies[1-7].

Gestational weight gain (GWG) is another important determinant for some other adverse outcomes, including SGA, LBW, and preterm birth[5, 8-11]. A systematic review showed that GWG below the recommendations was associated with higher risk of SGA and preterm birth[8]. A recent study reported higher risk of SGA among underweight pregnant women with inadequate GWG[9]. However, a previous study reported that pre-pregnancy body mass index (BMI) independently associated with SGA regardless of GWG[3]. Other reported associated factors for SGA and LBW included maternal smoking, maternal age, maternal anemia, and low socio-economic level[10, 12-14]. Although a few studies in Thailand also reported that pre-pregnancy underweight increased the risk of LBW and preterm birth, rate of SGA was not reported and GWG was not taken into account[15, 16]. A previous study at Siriraj Hospital showed that both pre-pregnancy underweight and inadequate GWG independently associated with SGA[17].

Both SGA and LBW newborns are at higher risk of perinatal short- and long-term morbidity and mortality, such as perinatal asphyxia, poor thermoregulation, hypoglycemia, polycythemia, impaired immune function, stillbirth and neonatal death, and impaired long-term neurodevelopment[18-20].

Currently, there is also limited information regarding this specific issue of GWG among underweight pregnant women and pregnancy outcomes at Siriraj Hospital. Therefore, the objective of this study was to compare the rate of SGA and LBW between underweight pregnant women who had adequate and inadequate GWG. In addition, factors associated with SGA and LBW were evaluated. Understanding the relationship between GWG and adverse outcomes among underweight women could help improving care and minimizing the risk associated with SGA and LBW in the future.

Materials and Methods

After approval from Siriraj Institutional Review Board, a retrospective cohort study was conducted in 300 singleton, underweight pregnant women (BMI < 18.5 kg/m^2) at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. Sample size was estimated based on a pilot study that showed rate of SGA among underweight pregnant women who gained adequate and inadequate weight were 8% and 20%, respectively. At 95% significance level and 80% power, using 1:2 ratio, at least 96 and 192 women with inadequate and adequate GWG were required. Inclusion criteria were singleton pregnant women who started antenatal care before 14 weeks of gestation and delivered at > 28 weeks of gestation. Exclusion criteria were women with chronic illness (diabetes, heart disease, hypertension, or thyroid disease, etc.), those who received medications such as corticosteriods or chemotherapy, and those with fetal anomalies. Study group consisted of 100 pregnant women with inadequate GWG and another 200 pregnant women with adequate GWG were randomly selected as a comparison group.

Pre-pregnancy BMI was calculated by measured height and weight before 12 weeks of gestation or self-reported pre-pregnancy weight. BMI category and adequacy of GWG were classified according to the Institute of Medicine (IOM) recommendation. Adequate GWG was defined as weight gain of 12.5 - 18 kg and inadequate weight gain was defined as weight gain of < 12.5 kg[21]. Gestational weight gain was calculated by subtracting pre-pregnancy weight from weight at delivery. Trimester-specific weight gain was also evaluated by determining weight differences between pre-pregnancy weight, weight at 14-16 weeks of gestation, weight at 26-28 weeks of gestation, and

weight at delivery.

Data was retrieved from medical records, including demographic data, antenatal care data, labor and delivery data, and pregnancy and neonatal outcomes. The main outcomes of interest were SGA, which was defined as infant birth weight of < 10th percentile for gestational age and LBW, which was defined as infant birth weight of < 2,500 g. Birth weight for gestational age percentiles was evaluated by World Health Organization (WHO) weight percentile calculator based on infant birth weight from the same population[22].

Descriptive statistics, including mean, standard deviation, number, and percentage were used to describe various characteristics as appropriate. Student t-test and chi-square test or Fisher's exact test were used to compare various characteristics between study and comparison groups. Logistic regression analysis was used to determine independent associated factors for SGA and LBW, adjusted for potential confounders. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated. A p value of < 0.05 was considered statistically significant.

Results

Of 300 underweight pregnant women included in this study, study group were 100 pregnant women with inadequate GWG whereas comparison group were 200 pregnant women with adequate GWG. Table 1 shows the comparison of baseline characteristics between the 2 groups. No significant differences were found in terms of maternal age, BMI, gestational age (GA) at first antenatal care (ANC), and parity. Rate of maternal anemia was slightly higher among cases than controls (20% vs. 14%) but without statistical significance (p = 0.181).

Table 1. Comparison of baseline characteristics between the 2 groups.

Characteristics	Adequate GWG n = 200 mean ± SD	Inadequate GWG n = 100 mean ± SD	p value
Age (years)	27.6 ± 5.8	26.7 ± 6.3	0.211
BMI (kg/m^2)	17.2 ± 1.0	17.0 ± 1.2	0.121
GA at first ANC (weeks)	9.6 ± 4.2	10.1 ± 4.7	0.357
	n (%)	**n (%)**	
Nulliparous	163 (67%)	63 (63%)	0.492
Anemia	28 (14%)	20 (20%)	0.181

GWG: gestational weight gain, SD: standard deviation, BMI: body mass index, GA: gestational age, ANC: antenatal care

Comparisons of trimester-specific weight gain between 2 groups are presented in Table 2. Mean GWG and each trimester weight gain (WG) in controls were significantly higher than those of cases (p < 0.001). Cases were also significantly more likely to have first trimester WG ≤ 2 kg (68% vs. 43%, p < 0.001), second trimester WG ≤ 7 kg (88% vs. 51.5%, p < 0.001), and third trimester WG ≤ 5 kg (64% vs. 35%, p < 0.001).

Comparisons of pregnancy outcomes are demonstrated in Table 3, women with inadequate GWG were significantly more likely to have LBW and SGA than those with adequate GWG (29% vs. 6%, p < 0.001, and 18% vs. 6.5%, p = 0.002, respectively). There were no significant differences between the 2 groups with regard to rates of primary cesarean section (CS), preeclampsia, and postpartum hemorrhage (PPH). Mean GA at delivery was significantly lower in cases than controls, but without clinical significance (38.0 ± 1.3 vs. 38.4 ± 0.9 weeks, p = 0.002). However,

cases were significantly more likely to have preterm delivery than controls (11% vs 2%, p = 0.001). In terms of neonatal outcomes, infant birth weight of study group was significantly lower than those of comparison group (2,752 ± 382.0 vs. 3,017 ± 333.8, p < 0.001). In addition, Infants of women in the study group were also more likely to have jaundice that requires phototherapy and hypoglycemia than those of comparison group (17% vs. 9%, p = 0.039, and 2% vs. 0%, p = 0.044, respectively). Both groups were comparable with regard to the rates of birth asphyxia and neonatal intensive care unit (NICU) admission.

Table 2. Trimester-specific weight gain between the 2 groups.

Weight gain	Adequate GWG n = 200	Inadequate GWG n = 100	p value
	mean ± SD	**mean ± SD**	
GWG (kg)	15.0 ± 1.6	10.2 ± 1.9	< 0.001
Trimester-specific weight gain			
First trimester WG (kg)	2.5 ± 1.5	1.3 ± 2.0	< 0.001
Second trimester WG (kg)	6.9 ± 1.7	5.1 ± 1.6	< 0.001
Third trimester WG (kg)	5.6 ± 1.8	3.8 ± 2.1	< 0.001
Trimester-specific weight gain with different cutoff	**n (%)**	**n (%)**	
First trimester WG 2 kg	86 (43%)	68 (68%)	< 0.001
Second trimester WG ≤ 7 kg	103 (51.5%)	88 (88%)	< 0.001
Third trimester WG ≤ 5 kg	70 (35%)	64 (64%)	< 0.001

GWG: gestational weight gain, SD: standard deviation, WG: weight gain

Table 3. Comparison of maternal and neonatal outcomes between the 2 groups.

Outcomes	Adequate GWG n = 200	Inadequate GWG n = 100	p value
Maternal outcomes			
Mean GA at delivery ± SD (weeks)	38.4 ± 0.9	38.0 ± 1.3	0.002
Preterm delivery	4 (2%)	11 (11%)	0.001
Primary C/S	63 (31.5%)	21 (21%)	0.076
Preeclampsia	6 (3%)	2 (2%)	0.612
PPH	4 (2%)	3 (3%)	0.589
Neonatal outcomes			
Mean birth weight ± SD (grams)	3,017 ± 333.8	2,752 ± 382.0	< 0.001
LBW	12 (6%)	29 (29%)	< 0.001
SGA	13 (6.5%)	18 (18%)	0.002
Apgar < 7 at 1 min	5 (2.5%)	4 (4%)	0.473
Phototherapy	18 (9%)	17 (17%)	0.039
Hypoglycemia	0 (0%)	2 (2%)	0.044
NICU admission	0 (0%)	1 (1%)	0.152

GWG: gestational weight gain, GA: gestational age, SD: standard deviation, C/S: cesarean section, PPH: postpartum hemorrhage, LBW: low birth weight, SGA: small-for-gestational age, NICU: neonatal intensive care unit

Logistic regression analysis was performed to determine independent associated factors for SGA and LBW and the results are shown in Table 4 and Table 5. After adjusting for confounding variables, the only independent associated factor of SGA was 2nd trimester weight gain < 7 kg (adjusted OR 9.92, 95%CI 2.06-47.68, p = 0.004), while the independent associated factor for LBW was inadequate GWG (adjusted OR 5.82, 95%CI 2.11-16.0, p = 0.001).

Table 4. Logistic regression analysis to determine independent associated factors for SGA.

Variables	Adjusted OR (95%CI)	p value
Maternal age 20 - 34 years	1.0	
Maternal age < 20 years	0.80 (0.21-3.09)	0.744
Maternal age ≥ 35 years	0.91 (0.27-2.98)	0.869
Multiparous	0.78 (0.32-1.93)	0.592
1st trimester weight gain ≤ 2 kg	2.29 (0.89-5.89)	0.087
2nd trimester weight gain ≤ 7 kg	9.92 (2.06-47.68)	0.004
3rd trimester weight gain ≤ 5 kg	2.04 (0.75-5.55)	0.163
Inadequate GWG	1.12 (0.41-3.10)	0.823
Anemia	0.35 (0.08-1.60)	0.175

SGA: small-for-gestational age, OR: odds ratio, CI: confidence interval, GWG: gestational weight gain

Table 5. Logistic regression analysis to determine independent associated factors for LBW.

Variables	Adjusted OR (95%CI)	p value
Maternal age 20 - 34 years	1.0	
Maternal age < 20 years	0.86 (0.27-2.72)	0.795
Maternal age ≥ 35 years	0.43 (0.12-1.56)	0.200
Multiparous	0.44 (0.18-1.07)	0.069
1st trimester weight gain ≤ 2 kg	1.49 (0.63-3.52)	0.365
2nd trimester weight gain ≤ 7 kg	1.02 (0.37-2.79)	0.970
3rd trimester weight gain ≤ 5 kg	1.14 (0.47-2.75)	0.771
Inadequate GWG	5.82 (2.11-16.0)	0.001
Anemia	0.69 (0.25-1.88)	0.469

LBW: low birth weight, OR: odds ratio, CI: confidence interval, GWG: gestational weight gain

Discussion

Underweight pregnant woman has been reported to increase risk of adverse pregnancy outcomes, including SGA[1-5], LBW[1, 2, 4, 15, 16], and preterm birth[1-4, 15, 16]. However, GWG should also be considered as another important determinant of such adverse outcomes, especially among these high-risk women.

The results of this study demonstrated that among underweight pregnant women, GWG below IOM recommendation increased the risks of SGA, LBW and preterm delivery compared to those with normal GWG. This was similar to what has been reported by many

previous studies. A previous systematic review of over 1 million pregnant women reported that GWG less than IOM recommendation significantly increased the risk of SGA and preterm delivery[8]. Other previous studies also reported that inadequate GWG increased the risk of SGA and LBW, regardless of pre-pregnancy BMI[3, 5]. However, the results of a recent systematic review supported the findings of this study that although no significant association between maternal pre-pregnancy BMI and SGA were observed, risk of SGA significantly increased among underweight women with inadequate GWG[9].

After adjusting for potential confounders, multivariate analyses demonstrated that second trimester weight gain of ≤ 7 kg independently increased risk of SGA by almost 10 folds. This was similar to previous studies which also reported that in the second trimester, insufficient weight gain was associated with SGA[23, 24] and LBW[10]. On the other hand, only inadequate GWG independently increased risk of LBW by almost 6 folds. This was comparable to the results of a previous systematic review which reported that inadequate GWG was associated with increased risks of LBW, in both developing and developed countries[25]. However, low weekly weight gain was associated with preterm birth, but not LBW[25].

Both SGA and LBW have been shown to increase various neonatal morbidities and mortality, such as stillbirth, hypoxic composite neonatal morbidity, and impaired childhood neurodevelopment, etc[18, 20, 26]. Therefore, understanding associated risk factors could help improve awareness for better surveillance and early identification which lead to appropriate management to improve neonatal outcomes. Not only being underweight increased the risks of adverse neonatal outcomes, the results of this study also signified the importance of GWG during pregnancy, especially during second trimester. According to the IOM recommendation, recommended weekly weight gain during the second and third trimester among underweight pregnant women should be 0.51 kg (0.44-0.58 kg)[21].

The exact mechanisms underlying the relationship between inadequate GWG and adverse pregnancy outcomes are still not known. However, this could probably be related to inadequate maternal nutritional status or nutritional transfer to the fetus. The effects might be more pronounced among underweight women. This should be further investigated and explored in future studies.

On the other end, gaining weight above recommendation has been reported to be associated with adverse outcomes in every pre-pregnancy BMI category, including LGA, macrosomia, and cesarean delivery[8, 11, 17]. In addition, lower rates of SGA and preterm birth have been reported among women who gained weight above recommendation from a systematic review[8]. However, currently there is still no recommendation for underweight women to gain more weight than recommended range to reduce adverse outcomes. Further evaluations are needed to determine appropriate weight gain ranges for each population.

Some limitations should be mentioned. Pre-pregnancy weight was obtained by self-report which might be inaccurate that there might be some misclassifications of BMI category. There might be some errors in obtaining trimester-specific weight gain due to differences in antenatal care schedule. However, such variations should not significantly alter the results. Generalization of the results might also be limited since the study was conducted in a single tertiary care hospital. Birth weight percentile was estimated based on the population of the hospital, which might not be representative of general population. For multiparous women, information on previous adverse pregnancy outcomes as well as changes in BMI after previous deliveries were not available and, therefore, were not taken into account in the analysis. The strength of the study may include the information on trimester-specific weight gain and it was taken into account in the analysis. Potential confounders were taken care of by multivariate analysis that independent associated factors were identified.

Being underweight and inadequate weight gain might only be a proxy to inadequate nutritional status. Actual nutritional status could not be evaluated in this study and more in-depth studies on this issue are needed to assess the relationship with adverse outcomes. Nonetheless, the results of this study could

be applied into clinical practice to improve care of underweight pregnant women. These at-risk women should be counseled and advised regarding appropriate and adequate nutrition during pregnancy. Weight gain monitoring is needed, especially during second trimester. Underweight pregnant women with inadequate weight gain should be further monitored closely for fetal growth and appropriate management should be provided in a timely manner.

Conclusion

In conclusion, being underweight independently increased the risk of LBW, while inadequate GWG independently increased risk of SGA among underweight pregnant women. Appropriate nutritional counseling should be provided and weight gain monitoring are needed. Keeping weight gain of these at-risk women could possibly help minimizing the risk of adverse outcomes.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Correlation between Regression of Postoperative CA125 Level in Epithelial Ovarian Cancer and 3-Year Progression Free Survival

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ABSTRACT

Objectives: To examine the relationship between regression of postoperative cancer antigen 125 (CA 125) level in epithelial ovarian cancer and 3-year progression free survival.

Materials and Methods: A retrospective study was conducted in patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I-IV epithelial ovarian cancer treated by complete surgical staging or primary debulking surgery between 2013 and 2017 at Prapokklao Hospital, Chanthaburi, Thailand. The study focused on pre-postoperative decline of serum CA 125 level. Three-year progression free survival analyses were conducted by the Kaplan-Meier method, log-rank test and multivariate Cox regression.

Results: A total of 125 epithelial ovarian cancer patients were enrolled as 38 patients with < 50% regression of CA 125, 41 patients with 50 - < 80% regression of CA 125 and 46 patients with ≥ 80% regression of CA 125. Survival analysis showed association between regression of CA 125 level and 3-year progression free survival ($p < 0.001$). Patients with ≥ 80% regression of CA 125 had better 3-year progression free survival than the 50 - < 80% and < 50% groups. [hazard ratio (HR) 50 - < 80% = 2.87 [95% confidence interval (CI): 0.90-9.13], HR < 50% = 5.34 [95%CI: 1.74-16.4] vs. ≥ 80% group].

Conclusion: Pre-postoperative regression of CA 125 had associated with 3-year progression free survival in patients who underwent primary surgery in epithelial ovarian cancer. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups.

Keywords: regression of postoperative CA125, epithelial ovarian cancer, progression free survival.

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ความสัมพันธ์ระหว่างค่า CA125 ที่ลดลงหลังผ่าตัดในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี

มานิตา รักตประจิต, นฤมล วิเชียรสมสกุล

บทคัดย่อ

วัตถุประสงค์: *เพื่อหาความสัมพันธ์ของการลดลงของ CA 125 หลังการผ่าตัดกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี ในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว*

วัสดุและวิธีการ: *รวบรวมข้อมูลจากแฟ้มเวชระเบียนและบันทึกการผ่าตัดของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งรังไข่ชนิดเยื่อบุผิวและได้รับการผ่าตัดระหว่างปีพ.ศ.2556 ถึง 2560 จำนวนทั้งสิ้น 125 คน เพื่อนำมาหาความสัมพันธ์ของค่า CA 125 ที่เปลี่ยนแปลงไปก่อนและหลังผ่าตัดกับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี โดยใช้ Kaplan-Meier method, log-rank test, และ multivariate Cox regression analysis ในการวิเคราะห์*

ผลการศึกษา: *จากการศึกษานี้มีผู้ป่วยเข้าเกณฑ์ทั้งหมด 125 คน แบ่งเป็นกลุ่มที่ CA 125 ลดลง ≥ ร้อยละ 80, ร้อยละ 50 ถึง < ร้อยละ 80, < ร้อยละ 50 จำนวน 46 คน, 41 คน, 38 คนตามลำดับ พบว่าค่า CA 125 ที่เปลี่ยนแปลงไปหลังการผ่าตัดมีความสัมพันธ์กับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี ($p < 0.001$) โดยกลุ่มที่ CA 125 ≥ ร้อยละ 80 จะมีระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรคนานมากกว่ากลุ่มร้อยละ 50 ถึง < ร้อยละ 80 และกลุ่ม < ร้อยละ 50 ตามลำดับด้วย hazard ratio (HR) ≥ 50 - < 80% = 2.87 ช่วงความเชื่อมั่น 0.90-9.12 และ HR < 50% = 5.34 ช่วงความเชื่อมั่น 1.74-16.42 เทียบกับกลุ่ม CA 125 ที่ลดลง ≥ ร้อยละ 80*

สรุป: *การลดลงของระดับค่า CA 125 ก่อนและหลังผ่าตัดในกลุ่มผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่ได้รับการผ่าตัดมีความสัมพันธ์กับระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค 3 ปี โดยกลุ่มที่ CA125 ≥ ร้อยละ 80 จะมีระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรคนานมากกว่ากลุ่มร้อยละ 50 ถึง < ร้อยละ 80 และกลุ่ม < ร้อยละ 50 ตามลำดับ*

คำสำคัญ: *CA 125 ที่เปลี่ยนแปลงไปหลังการผ่าตัด, มะเร็งรังไข่ชนิดเยื่อบุผิว, ระยะเวลาการมีชีวิตอยู่โดยปลอดการลุกลามเพิ่มของโรค*

Introduction

Ovarian cancer is the second most common type of female reproductive cancer and the sixth most common type of cancer in Thai women. The most common type of ovarian cancer is epithelial ovarian cancer[1]. Ovarian cancer has a high mortality rate and 14,240 out of 22,280 women in a 2016 study in the United States died from ovarian cancer[2].

Many indicators are used to diagnose ovarian cancer including risk of malignancy index (RMI), risk of ovarian malignancy (ROMA), or cancer antigen 125 (CA 125). Cancer antigen 125 or CA 125 is a high molecular weight glycoprotein coded from the MUC16 gene, which is overexpressed in epithelial ovarian cancer, causing Mullerian duct differentiation[3]. The cut-off value of CA 125 is 35 U/ml. The sensitivity of CA 125 ranges from 61 to 90%, with specificity of 71% to 93%, positive predictive value of 35% to 90% and negative predictive value of 67% to 90%[4]. The CA 125 indicator is commonly used but has certain limitations and can show false-positive results for diseases such as endometriosis, pelvic inflammation and other cancers.

Many attributes affect the prognosis of epithelial ovarian cancer such as residual tumor volume, volume of ascites, histologic subtype, stage, patient age and performance status[1]. CA 125 levels are influenced by several variables[5, 6]. But the serum CA 125 is a tumor marker that is measurable and commonly used in diagnosing and following-up the disease. It is important to monitor serum CA 125 levels and the change pattern of CA 125 levels for predicting prognosis[7]. A few previous studies have examined the correlation between changes in pre-postoperative CA 125 levels and progression free survival of the disease in the Thai population. This study examined the correlation between regression of pre-postoperative CA 125 levels in epithelial ovarian cancer and 3-year progression free survival.

Materials and Methods

Approval was given by the Ethics Committee of Prapokklao Hospital, Chanthaburi, Thailand to study the medical records and no informed consent was required.

This was a retrospective survival analysis study. Data were collected by reviewing medical records and operative notes of diagnosed 2014 the International Federation of Gynecology and Obstetrics (FIGO) stage I-IV epithelial ovarian cancer patients who underwent complete surgical staging or debulking surgery and received complete adjuvant management according to National Comprehensive Cancer Network (NCCN) guideline at the Department of Obstetrics and Gynecology, Prapokklao Hospital between January 2013 and December 2017. The data were reviewed along a 3-year clinical course from the date of surgery until imaging evidence of disease progression or event of disease-specific death. Exclusion criteria included inoperable patients, patients newly diagnosed ovarian cancer after recent surgical procedure without surgical staging, patients treated with neoadjuvant chemotherapy, patients diagnosed with endometriosis, patients diagnosed with other cell types of ovarian cancer (germ cell tumors, stromal tumors) and patients with no medical records regarding pre-postoperative CA 125, operative findings and pathological reports. The collected data included patients characteristics (age, body mass index, co-morbidities), tumor characteristics (histologic type, FIGO stage), specific data of primary surgery (presence of ascites, residual tumor after primary surgery, pre-postoperative serum CA 125 level) and follow-up data. The time from the date of primary cytoreductive surgery to the time of disease progression or cancer-related death in each patient was calculated follow-up time in months. Right censoring in this study concerned patients who lost to follow-up before recurrence or death during the 3-year clinical course.

The preoperative CA 125 levels were selected as closest to the date of surgery when more than one serum CA 125 level was documented. The postoperative CA 125 levels were obtained as close to the date of surgery as possible in early cancer stage patients who had observation and before the initiation of adjuvant therapy in advanced stage patients who had primary adjuvant chemotherapy. Pre-postoperative changes in

serum CA 125 levels were calculated as the absolute difference values. In addition, the percentage postoperative regression in CA 125 level was calculated for each patient. Based on previous studies[8], the study population was categorized into three groups as ≥ 80% reduction of CA 125, 50% - < 80% reduction of CA 125 and < 50% reduction of CA 125. Patients in whom the postoperative serum CA 125 level increased were included in the latter category. The outcome of primary surgery was categorized into three groups as complete (no residual tumor), optimal (residual tumor diameter ≤ 1 cm) and suboptimal (residual tumor diameter > 1 cm). The histology was categorized into four groups as serous, mucinous, endometrioid and clear cell.

The sample size was calculated at 122 patients by Stata software package, version 13.0. Using statistical values from a previous study, the hazard ratio of ≥ 80% reduction of the CA 125 group was 0.35 and censoring was 0.6[9]. Statistical analyses were to 80% power with alpha at 0.05. Continuous variables were presented as mean with standard deviation and median with interquartile range, while categorical variables were presented as numbers and percentages. Survival analyses were conducted by the Kaplan-Meier method and log-rank test. The relationships of other variables to progression free survival were determined by Cox regression analysis. Statistical significance was set at p value < 0.05.

Results

A total of 157 patients were diagnosed with epithelial ovarian cancer between January 2013 and December 2017. Two patients newly diagnosed ovarian cancer after recent surgical procedure without surgical staging and 17 treated by neoadjuvant chemotherapy were excluded. Patients with no medical records (operative note, preoperative CA 125, postoperative CA 125) were also excluded (Fig. 1).

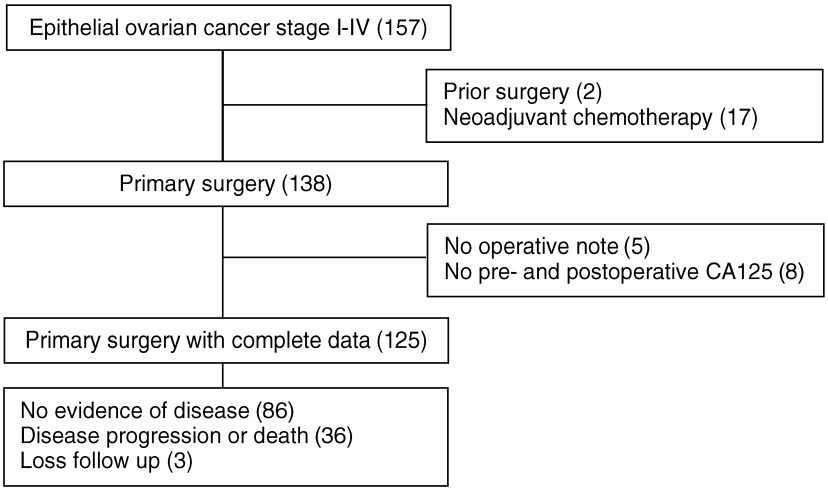


Fig. 1. Study flow.

Finally, 125 patients were enrolled and categorized into three groups according to percentage of CA 125 declination assessed in a previous study[5] as < 50%, 50 - < 80% and ≥ 80%. The 125 patients were enrolled as 38 patients with < 50% regression of CA 125, 41 patients with 50 - < 80% regression of CA 125 and 46 patients with ≥ 80% regression of CA 125. Four patients in whom the postoperative serum CA 125 level increased were included in the < 50% category. Most patients in the < 50% group (47.4%) and 50 - < 80% group (46.3%) were diagnosed with epithelial ovarian cancer FIGO stage III, while 50% of the ≥ 80% group were FIGO stage I. In all groups, most patients had optimal surgical outcome (50%, 43.9%, 45.7%) with no

ascites (55.3%, 61%, 56.5%). The most common cell type of the < 50% and 50 - < 80% groups was serous, whereas the ≥ 80% group was endometrioid. Median of preoperative CA 125 in each group were 251 U/ml, 86.80 U/ml and 420 U/ml, respectively. Median of absolute regression in CA 125 levels were 102.5 U/ml, 58 U/ml, 365 U/ml, respectively. Median times from serum preoperative CA 125 measurement to primary surgery were 27.5 days, 21 days and 29.5 days, respectively. Median times from surgery to serum postoperative CA 125 measurement were 30 days, 30 days and 32.5 days, respectively. The median follow-up time was 36 months. There were 5 of the 125 patients died from the ovarian cancer during the course of follow-up. Three patients lost to follow-up during the 3-year clinical course as right censoring in this study, including one patient from the 50 - < 80% group and two patients from the ≥ 80% group (Table 1).

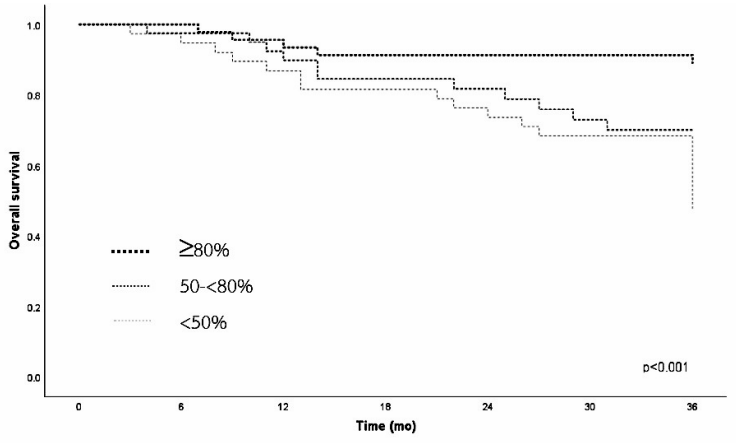
Table 1. Characteristic of the population.

Variable	CA 125 declination			
	< 50% (n = 38)	**50 - < 80% (n = 41)**	**≥ 80% (n = 46)**	**p value**
Age (years)*	53.61 ± 13.05	49.03 ± 14.27	51.78 ± 12.17	0.788
BMI (kg/cm^2) *	21.88 ± 3.65	21.74 ± 4.00	23.86 ± 4.92	0.763
FIGO stage†				0.094
I	12 (31.6%)	12 (29.3%)	23 (50%)	
II	0 (0%)	3 (7.3%)	5 (10.9%)	
III	18 (47.4%)	19 (46.3%)	13 (28.3%)	
IV	**8 (21.1%)**	**7 (17.1%)**	5 (10.9%)	
Surgical outcome†				0.819
No residual tumor	11 (28.9%)	17 (41.5%)	16 (34.8%)	
Optimal	19 (50%)	18 (43.9%)	21 (45.7%)	
Suboptimal	8 (21.1%)	6 (14.6%)	9 (19.6%)	
Histology†				0.074
Serous	17 (44.7%)	17 (41.5%)	10 (21.7%)	
Mucinous	9 (23.7%)	7 (17.1%)	8 (17.4%)	
Endometrioid	3 (7.9%)	9 (22.0%)	16 (34.8%)	
Clear cell	9 (23.7%)	8 (19.5%)	12 (26.1%)	
Ascites†				0.862
Negative	21 (55.3%)	25 (61%)	26 (56.5%)	
Positive	17 (44.7%)	16 (39%)	20 (43.5%)	
CA 125 (U/ml)‡				
Preoperative	251 (59.6-520.3)	86.8 (415-150.5)	420 (137.8-1147.50)	0.001
Postoperative	152.5 (62.8-314.0)	27 (14.3-57.5)	20.5 (10.0-44.28)	< 0.001
CA 125 change	102.5 (16.0-275.3)	58 (29.1-91.0)	365 (116.5-1044.0)	< 0.001
Time from CA 125 surgery (day)‡				
Preoperative CA 125	27.5 (15.5-32.8)	21 (14.0-32.0)	29.5 (14.8-39)	0.437
Postoperative CA 125	30 (28.5-40.3)	30 (29.0-58.0)	32.5 (29.8-50.5)	0.472
Event†				< 0.001
No evidence of disease	18 (47.4%)	29 (70.8%)	39 (84.8%)	
Disease progression or death	20 (52.6%)	11 (26.8%)	5 (10.9%)	
Loss to follow-up	0 (0%)	1 (2.4%)	2 (4.3%)	

*mean ± standard deviation, †n (%), ‡median (interquartile range)

BMI: Body mass index, FIGO: International Federation of Gynecology and Obstetrics

The Kaplan-Meier survival curve showed that the ≥ 80% regression CA 125 group had better survival outcome than the 50 - < 80% and < 50% groups (p < 0.001 by log-rank test) (Fig. 2). Multivariate Cox regression analysis with full adjustment by other prognostic factors for survival as mentioned showed that the percentage of CA 125 declination for the < 50% and 80% groups was associated with 3-year progression free survival. The 3-year progression free survival of < 50% regression of CA 125 was 5.34 time worse than the 80% group [HR<50% = 5.34 [95%CI: 1.74-16.42], p = 0.003 vs. the ≥ 80% group, p = 0.011]. Whereas the 3-year progression free survival of 50 - < 80% group was 2.87 worse but this was not statistically significant [HR50-<80% = 2.87 [95%CI: 0.90-9.12], p = 0.075] (Table 2).



Number at risk							
<50%	38	36	33	31	28	26	18
50-79%	41	40	37	35	34	31	30
≥80%	46	46	43	42	42	42	41

Fig. 2. Kaplan-Meier survival curves by categories of % postoperative regression in CA 125.

Table 2. Hazard ratio of % postoperative regression in CA 125.

CA 125 declination	unadjusted			Fully adjusted		
	HR	95%CI	p value	HR	95%CI	p value
< 50%	5.614	2.11-14.96	0.001	5.340	1.74-16.42	0.003
50 - < 80%	3.100	1.08-8.93	0.036	2.866	0.90-9.12	0.075
≥ 80%	1	-	0.002	1	-	0.011

Fully adjusted by age, BMI, FIGO stage, surgical outcome, histology, ascites

HR: hazard ratio, CI: confidence interval, BMI: body mass index, FIGO: International Federation of Gynecology and Obstetrics

Discussion

This study focused on the relationship between regression of CA 125 level in epithelial ovarian cancer and 3-year progression free survival. Results showed that pre-postoperative CA 125 declination of ≥ 80% group and the < 50% group were associated with 3-year progression free survival. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups, respectively. The < 50% regression of postoperative CA 125 had 5.34 time worse of disease prognosis compared to the ≥ 80% regression group.

This associated relation between pre-postoperative CA 125 declination and 3-year progression free survival in our study concurred with Timmermans et al and Zwakman et al[8, 9]. They studied the prognostic value of perioperative change in CA 125, and reported that the decline in serum CA 125 significantly associated with better survival. The study suggested that the perioperative decline in serum CA125 was an early biomarker that predicts disease-specific survival. According to Yoo et al[10], a study of the relationship between perioperative changes in serum CA 125 levels and progression free survival, our findings were in agreement with the results. The decrease of serum CA 125 levels ≥ 80% after surgery was a prognostic factor for progression free survival.

A strong point of our study was the similarity in characteristics of our population, accuracy of CA 125 and the confounding factor adjustment process. Baseline characteristics of each CA 125 declination group in our study were similar for age, body mass index, FIGO stage, surgical outcome, histology and ascites. The fact that CA 125 measurements at different times affects on postoperative CA 125 because of peritoneal trauma from abdominal surgery procedure[11]. Times from serum preoperative CA 125 measurement to surgery and times from surgery to postoperative CA 125 measurement of each group were also similar. Serum CA 125 level of our study had only a small effect on accuracy. Other prognostic factor adjustment in multivariate Cox regression analysis included body mass index and histology, which were different from Zwakman et al[9].

According to NCCN guideline[12], patients have to visit every 2-4 months for first 2 years and 3-6 months for 3 years for surveillance, this study might be used to assist gynecologist to choose on minimum duration of follow-up periods to accurately assess the recurrence of the disease.

However, our study had some limitations. This was a retrospective study and only 125 patients were enrolled because data collection was performed at a single center, while most complete medical records were available only from 2013.

When correlating the regression of postoperative CA 125 levels and 3-year progression free survival, the more percentage of declination in CA 125 had the better survival outcome. Future studies should include details from multiple centers with a longer data collection period to get more population and study more in role of adjuvant chemotherapy treatment in population that had < 50% CA 125 regression. To improve reliability, a prospective study should be undertaken including date of pre-postoperative CA 125 measurement, onset date of adjuvant chemotherapy and all other essential parameters.

Conclusion

Pre-postoperative regression of CA 125 had associated with 3-year progression free survival in patients who underwent primary surgery in epithelial ovarian cancer. The ≥ 80% CA 125 declination group recorded better survival outcome than the 50 - < 80% and < 50% groups. The < 50% regression of postoperative CA 125 had prognosis 5.34 times worse. To enable role of predicting 3-year progression free survival from regression of postoperative CA 125, more studies should be performed in large prospective studies.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Effectiveness of the Enhanced Recovery after Surgery (ERAS) Protocol Following Elective Cesarean Section: A single-center randomized controlled trial

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ABSTRACT

Objectives: To compare 24 hours postoperative recovery utilizing the quality of recovery questionnaire (QoR-35, Thai version) and pain assessment using the visual analogue scale (VAS) between pregnant women scheduled for elective cesarean section receiving enhanced recovery after surgery (ERAS) and standard protocol.

Materials and Methods: A randomized controlled trial was performed in 48 singleton pregnancy patients scheduled for elective cesarean section using the ERAS protocol and the standard protocol at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC). The 24-hour postoperative recovery and pain score were assessed to compare postoperative recovery. Postoperative complications after 72 hours postpartum were compared between two protocols.

Results: A total of 48 term-pregnant women were included in the study. Five women were excluded, leaving 43 participants (21 participants in the ERAS protocol group and 22 participants in the standard protocol group). As per the protocol analyses, the median (interquartile range (IQR)) of QoR-35 scores were 153.7 (± 10.2) and 149 (± 32), $p = 0.20$ in the ERAS group and standard group, respectively. The mean (± standard deviation (SD)) pain scores 24-hours postoperatively were 3.1 (±1.9) and 5.1 (±1.9), $p < 0.05$ in the ERAS and standard protocol groups, respectively. There was no postoperative complication reported.

Conclusion: There was no statistically significant difference between QoR-35 scores. However, the pain dimension with the ERAS protocol was significantly lower than in the standard care group and no complications were found 72 hours after surgery. The study found that the ERAS protocol was able to significantly reduce postoperative pain without increasing the negative impact on the surgical outcome.

Keywords: cesarean section, enhancing recovery, quality of recovery, pain.

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ประสิทธิผลโปรโตคอลเสริมการฟื้นตัว (ERAS) ในการผ่าตัดคลอด งานวิจัยแบบสุ่มมีกลุ่มควบคุม

ณัฐชา กลางประพันธ์, อมรินทร์ นาควิเชียร, จุฑารัตน์ เลื่อนผลเจริญชัย, วิภาดา เหล่าสุขสถิตย์

บทคัดย่อ

วัตถุประสงค์: *เปรียบเทียบการฟื้นตัวหลังผ่าตัดโดยแบบสอบถามคุณภาพการฟื้นตัวฉบับภาษาไทย 35 และประเมินความเจ็บปวดโดยเครื่องมือวัดความเจ็บปวดระหว่างหญิงตั้งครรภ์ที่นัดมาผ่าตัดคลอดในกลุ่มที่ได้รับการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัด (enhanced recovery after surgery (ERAS) protocol) และได้รับการดูแลตามมารตรฐาน (Standard protocol)*

วัสดุและวิธีการ: *การศึกษาเป็นแบบสุ่มและมีกลุ่มควบคุม ทำในประชากรหญิงตั้งครรภ์เดี่ยวที่นัดมาเพื่อผ่าตัดคลอดโดยได้รับการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) และได้รับการดูแลตามมารตรฐาน (Standard protocol) โดยเก็บข้อมูลจากผู้ป่วย 48 คน ที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯสยามบรมราชกุมารี ประเมินการฟื้นตัวหลังผ่าตัดที่ 24 ชั่วโมง และคะแนนความเจ็บปวดและเปรียบเทียบภาวะแทรกซ้อนหลังผ่าตัดที่ 72 ชั่วโมง ระหว่างการดูแลทั้ง 2 รูปแบบ*

ผลการศึกษา: *หญิงตั้งครรภ์ครบกำหนดในการศึกษาจำนวน 48 คน มีจำนวนผู้เข้าร่วมการศึกษา 5 คน ที่ถูกนำออกจากการศึกษาทำให้เหลือผู้เข้าร่วมการศึกษาจำนวน 43 คน แบ่งเป็นกลุ่มที่ได้รับการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัด (ERAS group) จำนวน 21 คน และกลุ่มที่ได้รับการดูแลตามมาตรฐาน (Standard group) จำนวน 22 คน การวิเคราะห์ข้อมูลในรายที่มีข้อมูลสมบูรณ์ (Per protocol analysis) ค่าเฉลี่ยคะแนนแบบสอบถามประสิทธิภาพการฟื้นตัวหลังผ่าตัวเท่ากับ 153.7 (±10.2) and 149 (± 32), p = 0.20 ในกลุ่มที่ได้รับการดูแลโดยใช้โปรโตคอล ERAS และกลุ่มที่ได้รับการดูแลตามมาตรฐานตามลำดับ และค่าเฉลี่ยคะแนนความเจ็บปวดที่ 24 ชั่วโมงหลังผ่าตัดเท่ากับ 3.1 (±1.9) และ 5.1 (±1.9), p < 0.05 ในกลุ่มที่ได้รับการดูแลโดยใช้โปรโตคอล ERAS และกลุ่มที่ได้รับการดูแลตามมาตรฐานตามลำดับ โดยไม่พบภาวะแทรกซ้อนหลังผ่าตัดของผู้เข่าร่วมการศึกษาทั้ง 2 กลุ่ม*

สรุป: *จากการศึกษาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างคะแนนแบบสอบถามประสิทธิภาพการฟื้นตัวหลังผ่าตัดฉบับภาษาไทยระหว่างกลุ่มที่ได้รับการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) และกลุ่มที่ได้รับการดูแลตามมาตรฐาน (Standard protocol) อย่างไรก็ตามด้านความเจ็บปวดหลังผ่าตัดพบว่ากลุ่มที่ได้รับการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัดมีคะแนนความเจ็บปวดที่น้อยกว่าอย่างมีนัยสำคัญทางสถิติและไม่พบว่ามีภาวะแทรกซ้อนหลังผ่าตัดที่ 72 ชั่วโมง การศึกษาพบว่าการดูแลโดยโปรโตคอลเสริมการฟื้นตัวหลังผ่าตัดสามารถที่จะลดความเจ็บปวดหลังผ่าตัดได้อย่างมีนัยะสำคัญทางสถิติโดยไม่พบผลลบต่อผลของการผ่าตัด*

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Introduction

Cesarean section is a life-saving surgical procedure, with its rate of use continuously increasing over the past decades. A study in Southeast Asia covering the period 1990 - 2014 demonstrated a total rate of cesarean section at 14.8%[1]. In Thailand, the rate of cesarean section increased from 20.7% in 2001 to 39.4% in 2014[2]. However, cesarean section is considered a complicated childbirth delivery and incurs a longer hospital stay and a 4 - 5 fold increase in maternal morbidity/mortality when compared to vaginal delivery[3]. Cesarean section morbidities, including infection, hemorrhage, gastrointestinal complications, and injuries to adjacent organs, are primarily related to the obstetrics and intraoperative conditions; albeit proper postoperative care is able to prevent and reduce the severity of the complications[4, 5]. There are a number of established interventions that promote recovery, including early ambulation, early feeding, and the reduction of postoperative pain. These practices can reduce the length of hospital stay, the cost of treatment, increase patient satisfaction and promote faster patient recovery[6-9].

The enhanced recovery after surgery (ERAS) protocol was first introduced in the 1990s by Dr Henrik Kehlet, a colorectal surgeon, to promote faster recovery and reduce the complications after surgery. Currently, ERAS guidelines have been developed for various procedures, including orthopedic, gynecologic oncology, pediatric, gastrointestinal/colorectal, and for breast, lung, and cesarean section surgery[10]. These protocols fasten recovery time by 30% and reduce complications by up to 50%[11]. The ERAS guidelines for cesarean section, published between 2018 - 2019, focus on the patient care process. The protocols include preoperative, intraoperative, and postoperative care to increase the efficiency of postoperative recovery[8, 12, 13]. Nevertheless, the effectiveness of the ERAS cesarean section protocol has been evaluated in only a few studies. To the best of our knowledge, no published or ongoing study comparing the treatment performance between pregnant women receiving the ERAS protocol and standard postoperative care has yet been conducted in Thailand. Consequently, we conducted a randomized controlled trial to compare the postoperative recovery effectiveness of pregnant women scheduled for cesarean section when using the ERAS protocol and when using the standard protocol. The effectiveness of recovery was determined at 24 hours postoperatively utilizing the quality of recovery questionnaire (QoR-35 Thai version, with permission from Pitimana-aree et al[14]. The questionnaire is designed to assess 5 dimensions of the patient's postoperative condition, i.e. comfort, emotional, physical independence, patient support, and pain, and is available in a Thai-translated edition with confirmed test validity (QoR-35 Cronbach's alpha 0.91). The QoR-35 is selected because it can assess multiple dimensions when compared with the other questionnaires reflecting more thorough evaluation of the patient recovery quality. Furthermore, this tool has been translated and modified to be appropriate to the Thai population. The safety aspects of the intervention, concerning the pain score and postoperative complications, were also evaluated.

Our objective was to compare the effectiveness of 24 hours postoperative recovery in pregnant women scheduled for elective cesarean section between the enhanced recovery after surgery (ERAS) protocol and the standard protocol. The recovery was assessed using the quality of recovery questionnaire (QoR-35, Thai version) while additional pain assessment was performed using the visual analogue scale (VAS).

Materials and Methods

A randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC), Srinakharinwirot University Hospital, during the period between June 2020 and December 2020. The research received appropriate approval from the institutional review board (IRB) (SWUEC-019/2563F). The study protocol was registered in the Thai Clinical Trial Registry (https://www.thaiclinicaltrial.org) (TCTR20210705001).

The sample size was estimated using the two-independent, continuous-outcome formula anticipating

an alpha of 0.5 and 80% power. The baseline QoR-35, as reported by Pitimana-aree et al[14] was 149.4 (±17). To detect a 10% increase plus 20% dropout, a total of 48 participants, 24 in each group, was required for the study. A total of 108 participants were assessed for eligibility, of whom 48 participants consented to participate and were randomly assigned to receive either the ERAS or the standard protocol. The study flow of participants was presented in Fig. 1. The participants were scheduled for elective cesarean section at 37 - 42 weeks' gestation, aged between 20 - 40 years old, and had conceived a singleton pregnancy without obstetrics or medical complications. Obstetrics complications were defined as either abnormal placentation (placenta previa or placenta accrete syndrome) or pregnancy-induced medical complications, such as gestational diabetes or hypertensive disorders in pregnancy. Medical complications included existing pre-gestational medical illnesses that required medication treatment. The participants were not contraindicated for using cefazolin, non-steroid anti-inflammatory drugs (NSAIDs), or metoclopramide. Women who subsequently either had a postpartum hemorrhage, received (or were converted to) general anesthesia, underwent an emergency cesarean section, or demonstrated unstable postoperative conditions (shock, anaphylaxis, respiratory distress) were excluded from the trial. Information regarding the study was given during antenatal visits. Written informed consent was obtained from all participants at their admission (1 day prior to the operation). The participants were then randomly assigned into 2 groups: those receiving either ERAS or standard postoperative care, using a block randomization (block of four) method.

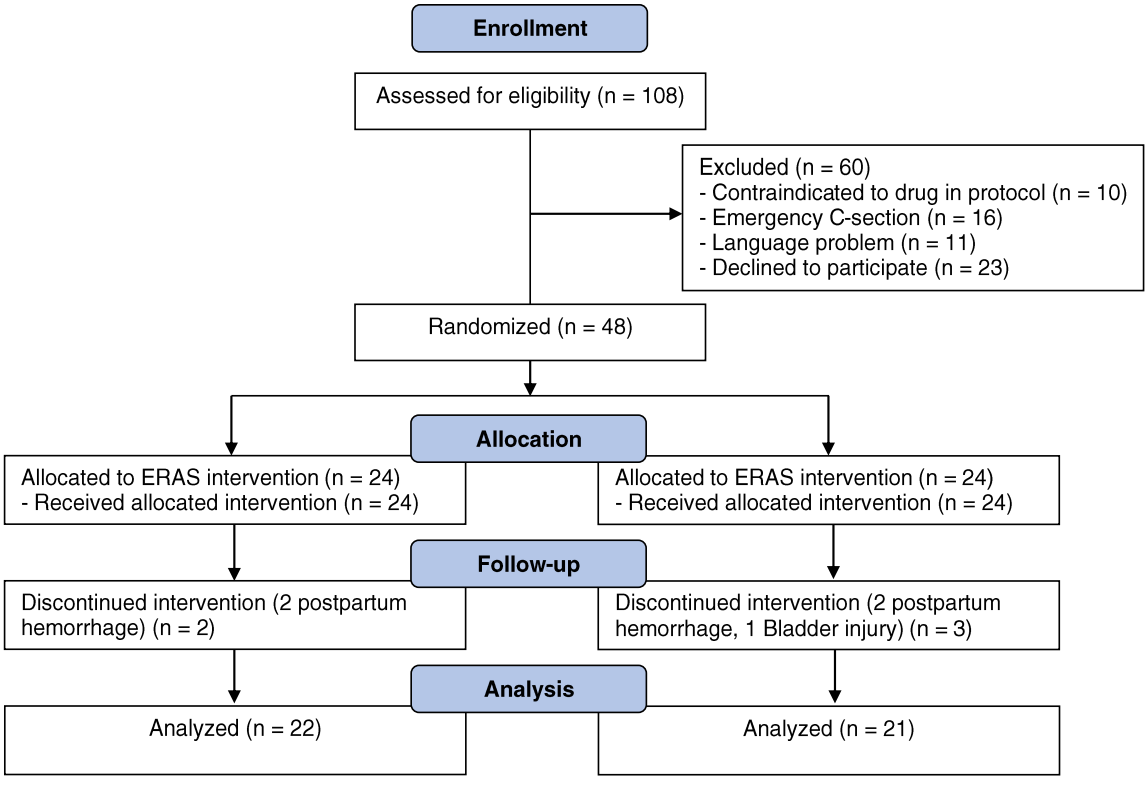

Fig. 1. Study flow of the participants.

Detailed information regarding both the operative protocols is provided in Table 1. All the participants received the same preoperative preparation, except patients in the ERAS group were given 50 ml water

containing 50 gm glucose at 6:00 am on the day of the surgery. Spinal anesthesia was performed by an anesthesiologist using 10 mg of 0.5% heavy bupivacaine with 0.2 mg morphine. The ERAS participants received prophylactic 10 mg metoclopramide given intravenously, while the participants in the standard protocol group were given an antiemetic drug upon request when showing symptoms. All the patients were observed in the recovery room for 2 hours post-operation and then were moved to a postpartum ward. Early ambulation was advised for all the patients in both groups. In the ERAS group, the participants were promptly provided with fluids and food along with analgesic medication (oral paracetamol 500 mg every 6 hours and ibuprofen 400 mg every 8 hours), once the postoperative vital signs were stabilized. Nonetheless, all the participants could request additional pain control regardless of their study group, with all additional medications further recorded. All medications from the study protocol and additional pain control were recorded and examined to assess the patient compliance and contamination of treatment protocol. To decrease the contamination of treatment, the case is indicated in which form of care using the patient chart symbol. The participants were unblinded with intervention, but the outcome assessors were blinded from the study protocol.

Table 1. Components of intervention between ERAS and standard protocol in cesarean delivery.

ERAS protocol	Standard protocol
Preoperative	**Preoperative**
Explain the indications for the procedure, the preparation before surgery, the possible complications, and the recovery time after surgery Giving patients water to drink: a solution containing 50 gm of glucose in 50 ml of water at 6.00 am on the day of surgery	Explain the indications for the procedure, the preparation before surgery, the possible complications, and the recovery time after surgery NPO after midnight
Intraoperative	**Intraoperative**
Anesthesia by spinal anesthesia, euvolemic status, and prevention of hypothermia	Anesthesia by spinal anesthesia, euvolemic status, and prevention of hypothermia
Metoclopramide 10 mg intravenous after spinal anesthesia	Giving the patient an antiemetic drug if the patient feels nausea or vomiting after spinal anesthesia
Purify the skin around the surgery with an antiseptic	Purify the skin around the surgery with an antiseptic;
Apply antibiotic prophylaxis (cefazolin) 30 - 60 minutes before the procedure before surgery	Apply antibiotic prophylaxis (cefazolin) 30 - 60 minutes before the procedure before surgery
Postoperative	
Giving patients the ability to eat water and food immediately after surgery 2 hours after the general symptoms and vital signs stabilize	Step diet after surgery.
Paracetamol 500 mg given every 6 hours with NSAIDs (ibuprofen 400 mg) every 8 hours	Giving paracetamol painkiller at 500 mg according to the patient pain and adding other painkillers if this did not provide enough pain relief
Extra analgesics: tramadol 50 mg IV prn every 8 hours	Extra analgesics: tramadol 50 mg IV prn every 8 hours
Early ambulation	**Early ambulation**
Removal of the urinary catheter 6 hours after surgery	Removal of the urinary catheter 12-24 hours after surgery

ERAS: enhanced recovery after surgery, IV: intravenous, PRN: pro re nata

The quality of recovery was evaluated using the QoR-35 (Thai version) 24-hours postoperatively. The QoR-35 is a self-evaluation questionnaire consisting of 35 questions, worth 5 points each, so 175 points in total, divided into 5 dimensions, as mentioned above. A high total score indicates a good postoperative recovery performance. Concurrently, the pain score was assessed using the VAS. All the participants were hospitalized for at least 72 hours post-operation according to the original departmental policy, unless there was a complication. The participants were asked to visit either a hospital or clinic in their neighborhood to assess the surgical wound at 7 days following the surgery. All the participants visited the clinic at MSMC at 6 weeks for postpartum follow-up. The wounds and puerperium complications were recorded.

Statistical analysis

Descriptive statistics: the mean (standard deviation (SD)), median (interquartile range (IQR)), or proportion (%) were used where appropriate. Either the student t test, Mann - Whitney U test, or chi square

test was used when appropriate to detect differences in the variables between the intervention groups. The study was planned for per-protocol analysis. Comparison of both the mean QoR-35 (primary outcome) and pain score (secondary outcome) at 24-hours postoperatively was done by the student t-test method. The convergent validity of the Thai version of QoR-35 was reported in the literature[14]. The incidences of postoperative complications were compared using the chi-square test. A p value of 0.05 was determined significant and the 95% confidence interval (CI) was estimated. All the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 23.0 (IBM, New York).

Results

In total, 48 term-pregnant women participated in the study and were equally and randomly assigned into 2 groups. Five women were excluded, comprising 4 with postpartum hemorrhage (2 from each group) and 1 from the standard group with intraoperative bladder injury. The remaining 43 women completed the study protocols, non-contamination of treatment observed, were included in the outcome analysis. All 43 participants visited the hospital for post-partum check-up and were thus able to participate in the study. At 6-week follow-up, no participant showed postpartum complications. The participants' mean age was 31.2 (± 5.5) years with a mean gestational age of 38.7 (± 0.5) weeks gestation. The main surgical indications were previous cesarean section (93.7 %), and breech presentation (6.3%). The average surgical time was 64.20 (± 17.65) minutes and the participants had an average blood loss of 560 (± 196.76) ml. Table 2 compares the demographic data between participants from the ERAS and standard protocols groups. There were no significant differences in both the general and operative data between the two groups.

Table 2. Baseline patient characteristics.

Characteristics	ERAS group (n = 24)	Standard group (n = 24)	p value
General information			
Maternal age (years)			
mean (SD)	32.5 (5.4)	29.9 (5.3)	0.10
BMI (kg/m^2)			
mean (SD)	25.0 (5.1)	26.2 (5.2)	0.42
Income (THB/month)			
15,000 - 29,999: n (%)	14 (58.3%)	18 (75%)	0.12
more than 30,000: n (%)	10 (41.7%)	6 (25%)	
Operative information			
Skin incision			
Low midline incision: n(%)	3 (12.5%)	1 (4.2%)	0.29
Pfannenstiel incision: n (%)	21 (87.5%)	23 (95.8%)	
Fetal presentation			
Vertex: n (%)	23 (95.8%)	22 (91.7%)	0.55
Breech: n (%)	1 (4.2%)	2 (8.3%)	
Previous cesarean delivery: n (%)			
0	1 (4.2%)	2 (8.3%)	0.24
1	17 (70.8%)	18 (75%)	
2	5 (20.8%)	4 (16.7%)	
3	1 (4.2%)	0 (0%)	
Operative times (minutes)			
mean (SD)	63.7 (17.5)	64.2 (17.0)	0.92
Operative blood loss (ml)			
median [IQR]	500 [277.5]	600 [287.5]	0.24

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

Concerning the primary outcome, the participants' recovery scores (QoR-35) were not significantly different between the two groups, although there was a higher trend noted in the ERAS group (median [IQR] 153.5 [14.5] vs. 149 [32], p = 0.20). Breakdown of the QoR-35 scores are shown in Table 3. There was no significant difference between the groups in all aspects, except for the pain dimension. The ERAS group demonstrated better pain control compared to the standard protocol (median [IQR]: 25.5 [4] vs 24 [5], p < 0.05).

Table 3. Detailed analysis on each QoR-35 dimension.

Dimension	ERAS group	Standard group	p value*
Comfort dimension			
median score [IQR]	52.5 [8.2]	53 [8.5]	0.76
Emotional dimension			
median score [IQR]	30.5 [5.2]	30 [7]	0.59
Physical dimension			
median score [IQR]	19.5 [2.5]	17 [7]	0.09
Support dimension			
median score [IQR]	29 [4.2]	29 [6]	0.86
Pain dimension			
median score [IQR]	25.5 [4]	24 [5]	< 0.05

* Mann–Whitney U test, ERAS: enhanced recovery after surgery, IQR: interquartile range

Correspondingly, the mean pain scores at 24 hours following cesarean section were significantly lower in the ERAS group when compared to the control standard postoperative care (mean (SD): 3.1 (1.9) vs. 5.1 (1.9); mean difference 2.0, 95% CI 0.8, 3.2, p < 0.05). Regarding the additional opioid use, the rate of opioid use in the ERAS group was 9.09% when compared to the 38.09% in the standard protocol (p < 0.05). Opioid doses administered 24-hours postoperatively were significantly lower in the ERAS group in comparison to in the standard protocol group. Neither immediate, 72-hour postoperative, nor 6-week postpartum complications were observed in all participants. Pain evaluation at 24 hours postoperatively was assessed by VAS (Table 4).

Table 4. Pain scores between protocol.

Pain score	ERAS group (n = 22)	Standard group (n = 21)
0-3	13 (59.1%)	5 (23.8%)
4-6	8 (36.4%)	9 (42.9%)
> 6	1 (4.5%)	7 (33.3%)

ERAS: ehanced recovery after surgery

Discussion

This randomized controlled study did not observe a significant improvement in the quality of recovery (QoR), despite observing a higher trend with the ERAS protocol. However, pain control at 24 hours after surgery, determined by both the QoR-35 pain dimension and the VAS, was significantly better in the patients in the ERAS. Although, more acetaminophen and ibuprofen were used during the first 24 hours, the rate of opioid usage in the ERAS protocol group was significantly lower than in the standard group (9.09% vs. 38.09%, p < 0.05).

Effective perioperative care is paramount for the successful prevention of postoperative complications, and reduction of the length of hospital stay and cost of treatment. Quality of the patient recovery can be determined in various aspects by a variety of tools; for example: i) activities of daily living (ADLs), ii) visual

analogue scale of recovery (VAS-R), and QoR-35 . The authors selected the QoR-35 for two reasons; first, it assesses five dimensions of a patient's recovery, namely comfort, emotional, physical independence, support, and pain, and second, the questionnaire was already available with a Thai-translated edition with confirmed test validity[15]. We also backed this up with the pain VAS to evaluate pain control, which is a major concern of both physicians and patients, along with the incidence of postoperative complications at 72 hours (during admission). The length of hospital stay was otherwise not included in the analysis because it is common practice in Thailand for patients to stay in the hospital for at least a fixed minimum of 72 hours according to the local guidelines.

To the best of our knowledge, this is the randomized control trial to evaluate the effectiveness of the ERAS protocol in elective, considered uncomplicated, cesarean section in Thailand. The sample size was calculated, and the study population encompassed a low rate of participant dropout and no postoperative complications. Nonetheless, we did not observe a difference in the overall QoR-35 scores. Our primary outcome finding contrasted with other studies showing that the ERAS protocol could enhance patient recovery[8, 12, 13], although these studies did not use the QoR-35 questionnaire. It is noteworthy that there were a few modifications in our ERAS protocol due to differences in the institutional context; for example, giving drinking water until 2 hours prior to the surgery was not used in our study. Moreover, despite being one of the major operations, cesarean section may spare some recovery aspects assessed by the questionnaire; thus, overall differences were not obvious. The sample size estimation was calculated to detect a 10% difference; however, in the current study we did observe such a sized difference, only a 5.64% QoR-35 higher in the ERAS group. The post-hoc analysis demonstrated that our use of the QoR-35 to assess effectiveness of recovery after cesarean section was under-power to detect a difference between the protocols, due to the reasons stated above. A questionnaire developed specifically to assess postoperative recovery in cesarean section would be more appropriate. Nonetheless, we suggest reconsidering to use all dimensions of QoR-35 to evaluation the postoperative recovery. Because some dimension such as emotional state or psychological support may affected by variable factors other than protocol intervention.

Nevertheless, an improvement in terms of pain control was observed in the current study. It is important to emphasize that, by using acetaminophen and NSAIDs, the ERAS could reduce the opioid (in our institution, tramadol) use by approximately 4 times. Our findings are supported by other evidence in the literature. Hedderson and colleague also demonstrated that the ERAS protocol could reduce opioid usage after cesarean delivery[16]. Moreover, a meta-analysis conducted in parallel to our study by Meng, et al showed that the ERAS could reduce postoperative pain and opioid use[17]. It is known that use of opioid postoperatively can produce various unfavorable effects, such as respiratory depression, nausea and vomiting, bowel dysfunction, urinary retention, and pruritus[18]. Two recent randomized controlled trials (RCTs)[19, 20], however, observed no difference in terms of narcotic used but the pain assessed by VAS was significantly reduced in the one study[20]. In our study, pain assessment as part of the QoR-35 also demonstrate 1.5 points mean difference referring to a more satisfaction in regards of pain control, i.e. less pain breakthrough. To sum up, data from our and other studies could therefore establish a conclusion that the ERAS is more superior in the pain-control aspect when compared to the standard post-operative protocol. Therefore, the decrease in opioid use is a result of pain control from the ERAS protocol. The advantage of this questionnaire was pain assessed focused during 24 hours after operation, pain assess-analgesic drug interval was unimportant. In different, the pain evaluated by VAS may influence. In term of additional opioid administration, we found that multimodal analgesia can reduce postoperative pain and reduce opioid use.

Other benefits of the ERAS following cesarean section reported in the literature are a reduction of the length of hospital stay and an improved cost-effectiveness[21-24]. As aforementioned, the study was conducted in such a way so as not to interfere with the

local practice in terms of the hospital stay; thus, we did not include the length of stay and the cost in the analysis. The authors, however, will promote further trials in the future, especially in an institution/situation where postpartum beds are limited.

The results showed that those who were unable to follow the protocol were not used for analysis. The results of the study may be inferred that the outcomes of the protocols were different depend on the patient care. However, the study did not assess patient satisfaction, which could inform the effectiveness of the ERAS protocol in another way. Therefore, if the ERAS protocol can be used for pregnant patients in Thailand, the researcher expects that although the treatments are not significantly different, we can take advantage from the control pain process.

Conclusion

In conclusion, the ERAS protocol enhanced patient recovery following elective cesarean section, at least in the pain control aspect and without causing harm to the patient. Further studies with larger participants are encouraged to evaluate other aspects of 'quality recovery'. More studies should also be carried, with a few modifications to the protocol, for other forms of surgery, e.g., emergency cesarean section.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Enhanced Recovery after Surgery Protocol and the Factors Associated with Prolonged Hospitalization in Major Gynecologic Surgery at Suratthani Cancer Hospital

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ABSTRACT

Objectives: To evaluate the effectiveness and safety of our adopted enhanced recovery after surgery (ERAS) program for elective major gynecologic surgery at Suratthani cancer hospital and identified the factors contributing to prolonged hospitalization.

Materials and Methods: In this retrospective study, all patients who underwent major gynecologic surgery at Suratthani cancer hospital from July 2016 to December 2020 were included. We defined prolonged length of stayed group as those above medians of length of hospitalization and identified the risk factors that associated to this group.

Results: Two hundred and fifty patients who underwent major gynecologic surgery at Suratthani cancer hospital, were included. The median length of post-operative hospital stay was 3 days. And 86 (34.4%) patients have more than 3 days of post-operative hospital stay. The factors that associated with prolonged hospital stay were high body mass index (BMI), high American Society of Anesthesiologists (ASA) classification, disease of cervix, Radical hysterectomy with pelvic node dissection (RHND) operation, extremely blood loss, prolonged operative time and complication from surgery.

Conclusion: Our ERAS program showed some potentials of patient care in major gynecologic surgery. The risk factors that associated with prolonged hospital stay in this study were mostly non-modifiable. This result will be used to improve our ERAS program and promote the ERAS program in major gynecologic surgery.

Keywords: ERAS, hospitalization, length of stayed, major gynecologic surgery.

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โปรแกรมส่งเสริมการฟื้นฟูหลังผ่าตัดทางนรีเวชในโรงพยาบาลมะเร็งสุราษฎร์ธานี และปัจจัยที่ส่งผลต่อความล่าช้าในการจำหน่ายผู้ป่วย

กาญจนา กันธิยะ, สรวัจน์ เจนวณิชสถาพร

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพและความปลอดภัยของโปรแกรมส่งเสริมการฟื้นฟูหลังผ่าตัดที่ปรับเพื่อมาใช้ในการผ่าตัดผู้ป่วยทางนรีเวชในโรงพยาบาลมะเร็งสุราษฎร์ธานี และประเมินปัจจัยที่มีผลต่อความล่าช้าในการจำหน่ายผู้ป่วย*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลัง โดยนำผู้ป่วยที่ได้รับการผ่าตัดทางนรีเวชในโรงพยาบาลมะเร็งสุราษฎร์ธานี ตั้งแต่ กรกฎาคม 2559 ถึง ธันวาคม 2563 และได้จำแนกผู้ป่วยที่นอนโรงพยาบาลนาน คือกลุ่มที่มากกว่าค่ามัธยฐาน และศึกษาปัจจัยที่มีผลต่อความล่าช้าในการจำหน่ายในผู้ป่วยกลุ่มนี้*

ผลการศึกษา: *ผู้ป่วยจำนวน 250 ราย ที่ได้รับการผ่าตัดทางนรีเวชในโรงพยาบาลมะเร็งสุราษฎร์ธานี พบว่ามัธยฐานของวันเฉลี่ยที่นอนโรงพยาบาลอยู่ที่ 3 วัน และ 84 ราย (ร้อยละ 34.4) นอนโรงพยาบาลนานกว่า 3 วัน และพบปัจจัยที่มีผลต่อความล่าช้าในการจำหน่ายผู้ป่วย ได้แก่ ดัชนีมวลกายที่สูง, การประเมินสมรรถภาพของผู้ป่วยก่อนการผ่าตัดที่สูง, โรคที่เกี่ยวกับปากมดลูก, การผ่าตัดมดลูกออกแบบถอนรากถอนโคน, การเสียเลือดมาก, ระยะเวลาการผ่าตัดที่ยาว และมีภาวะแทรกซ้อนจากการผ่าตัด*

สรุป: *โปรแกรมส่งเสริมการฟื้นฟูหลังผ่าตัด ในการผ่าตัดทางนรีเวชในโรงพยาบาลมะเร็งสุราษฎร์ธานีมีผลลัพธ์ที่ดี โดยผู้ป่วยส่วนใหญ่สามารถจำหน่ายได้เร็ว และมีภาวะแทรกซ้อนกับอัตราการมานอนโรงพยาบาลซ้ำที่ต่ำ จากข้อมูลนี้จะช่วยพัฒนาโปรแกรมส่งเสริมการฟื้นฟูหลังผ่าตัด ของเราให้ดีขึ้น และสนับสนุนให้โรงพยาบาลอื่นใช้โปรแกรมนี้มากขึ้น*

คำสำคัญ: *โปรแกรมส่งเสริมการฟื้นฟูหลังผ่าตัด Enhanced recovery after surgery (ERAS) program, ระยะเวลาการนอนโรงพยาบาล, การผ่าตัดทางนรีเวช*

Introduction

Enhanced recovery after surgery (ERAS) was first outlined by a Danish surgeon, Dr. Henrik Kehlet in 1995 for colorectal surgery[1]. It is the evidence base multimodality protocol that aim to migrate the physiologic stress and optimize the rehabilitation of patient. Numerous publications have validated its efficacy to reduced hospital stay and complication rate[2].

In the recent years, ERAS protocol has been adopted in several other fields of surgeries[3-6]. ERAS protocol for gynecologic surgery also showed promising outcome. The previous studies showed postoperative hospital length stay in ERAS group that was shorter than the conventional group, 6.5 ± 3.5 days and 10.7 ± 11.4 days, respectively[7]. Meta-analysis demonstrated a 1.6 days decrease in length of stay (LOS), 32% reduction in complications and a 20% reduction in readmission (odds ratio (OR) 0.80, 95% confidence interval (CI) 0.64-0.99) for ERAS patients[8]. However ERAS protocol still underused in gynecologic surgery. Data from an international survey showed only 33% of institution that ERAS protocol was implemented and only 19% in asia[9].

Suratthani cancer hospital is the tertiary referral cancer center in the southern region 11 of Thailand. The ERAS protocol for gynecologic surgery was implemented and adapted to patients since the gynecologic oncology department was established in 2016. The purpose of this study was to evaluate effective and safety of our ERAS program for elective gynecologic surgery and identified factors associated with prolonged hospitalization. The results may guide to develop intervention to the target at risk patients, improve overall care, and reduce resource utilization.

Materials and Methods

We conducted a retrospective study using collected data included all patients who underwent elective major gynecologic surgery at Suratthani cancer hospital from July 2016 to December 2020.

Inclusion criteria was 18 or more-year-old patients who underwent elective major gynecologic surgery at Suratthani cancer hospital. Exclusion criteria were 1) patients whose data were lost and 2) patients who were referred to another hospital during admission.

Our ERAS protocol was adopted and developed from ERAS® society guideline10 that are detailed in Table 1.

The sample size was calculated with the formula for descriptive study using confidence level of 95% and 5% margin of error and proportions of prolonged hospital stay from a study proposed by Agrawal et al[11]. The minimal sample sizes were 236 cases.

The data were collected, and medical records were reviewed. The collected data included age, weight, height, underlying disease, diagnosis, operative detail, length of stay, and postoperative morbidity and mortality. We allocated the patients into two groups by using medians of length of post-operative hospital stay. Firstly, patients in normal length of stay (NLOS) group and secondly, patients in prolonged length of stay (PLOS). NLOS were defined as those equal or below medians of length of post-operative hospital stay and PLOS were defined as those above medians of length of post-operative hospital stay.

Statistical analyses included descriptive and inferential statistics. Variables were described using frequency and percentages for categorical data and mean, standard deviation (SD), median, interquartile range (IQR) for quantitative data. In comparison of 2 groups, categorical variables were analyzed using chi-square test. Continuous data were analyzed by using the student t-test for the data with normal distribution, and Mann-Whitney U test for the data with non-normal distribution. OR ratio was calculated with binary logistic regression analysis. A p value less than 0.05 was considered as statistically significant. Data were analyzed using SPSS® version 22.0 for Windows®.

Table 1. Enhanced recovery after surgery (ERAS) Protocol.

Preoperative	Give operative information
	Nutritional screening and treatment
	Give antidepressant as needed
	No routine mechanical bowel preparation
Intraoperative	Control excessive bowel exposure
	Prophylaxis antibiotic
	Prophylaxis VTE prevention with Enoxaparin SC (if no contraindicated)
	Locoregional anesthesia
	Epidural block
	Local injection
	Abdominal tap block
Postoperative	Promote early ambulation
	24 hr after surgery – sit or upright position
	48 hr after surgery – walk
	Promote respiratory exercise
	Early taking oral diet
	Day after surgery – oral fluid intake
	24 hr after surgery – soft diet
	Minimized intravenous fluid, keep urine output at 0.5-1 ml/kg/hr
	Multimodality analgesia
	Acetaminophen prescribed every 4 hours
	NSAIDs for selected case
	Reduced opioid use
Discharge criteria	No fever or tachycardia
	No clinical complication
	Ambulation with minimal assistance
	Adequate pain control with oral analgesia
	Adequate hydration and nutrition intake

VTE: venous thromboembolism, SC: subcutaneous, NSAIDs: non-steroidal anti-inflammatory drugs

Results

There were 258 patients who underwent elective gynecologic surgery patients at Suratthani cancer hospital from July 2016 to December 2020. Eight patients were excluded due to referred to other hospital during admission: 3 patients were required ICU after surgery, 4 patients had the condition that required internal medicine physician care and 1 patient had intraoperative complication. Therefore, a total of 250 patients were included for analysis in this study. (Fig. 1)

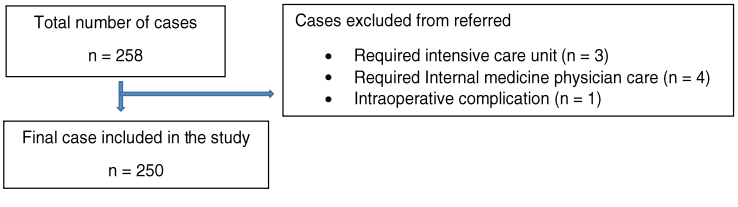

Fig. 1. Detail of patients.

The demographic and characteristics of the patients are shown in Table 2. A total of 250 patients with a mean age of 49 years (range 19 - 84 years), the mean body mass index (calculated as weight (kg)/ height (m^2)) was 25.1 kg/m^2. While most cases did not have underlying (64%) and 56% of the cases were diagnosis malignancy. More than half of cases had an ASA (American Society of Anesthesiologists) classification of 2. Most patients (86%) received general analgesia (GA), 9.6% of patients received GA combined with regional analgesia (RA) and 1.2% of patients received only RA. Most patients underwent surgical staging and follow by total abdominal hysterectomy with bilateral salpingo-oophorectomy, salpingo-oophorectomy, radical hysterectomy with pelvic node dissection, and total abdominal hysterectomy. 26 patients used patient controlled analgesia (10.4%). Mean overall morphine dosage was 5.6 mg (SD ± 4 mg).

Postoperative complications was 4% with bleeding 2 cases, bowel eviscerated 1 case, respiratory complication 4 cases, femoral nerve neuropraxia 2 cases, and vesicovaginal fistula 1 case. One patient had hospital readmission within thirty days of discharge due to retained foreign body.

Table 2. Characteristic of patients (n = 250).

Age (years)	Mean 49.3 (SD ± 12.6)
< 40	56 (22.4%)
40 - 59	142 (56.8%)
60 - 80	52 (20.8%)
BMI (kg/m^2)	Mean 25.1 (SD ± 5.61)
< 20	26 (10.4%)
15 - 25	108 (43.2%)
25 - 30	65 (26%)
> 30	49 (19.6%)
Underlying disease	
No	160 (64%)
Hypertension	65 (26%)
Diabetes mellitus	27 (10.8%)
Pulmonary disease	9 (3.6%)
Other cancer	4 (1.6%)
Other disease	9 (3.6%)
Menopause	118 (47.2%)
ASA classification	
1	83 (33.2%)
2	142 (56.8%)
3	25 (10%)
Diagnosis	
Ovarian neoplasm	112 (44.8%)
Benign	61 (24.4%)
Borderline	8 (3.2%)
Malignant	43 (17.2%)
Uterus neoplasm	100 (40%)
Benign	33 (13.2%)
Malignant	67 (26.8%)

Table 2. Characteristic of patients (n = 250). (Cont.)

Cervix neoplasm	38 (15.2%)
Benign	4 (1.6%)
Carcinoma in situ (CIS)	4 (1.6%)
Malignant	30 (12%)
Pathology	
Benign	98 (39.2%)
Borderline or CIS	12 (4.8%)
Malignant	140 (56%)
Stage 1	98 (39.2%)
Stage 2	16 (6.4%)
Stage 3	15 (6%)
Stage4	11 (4.4%)
Operation	
TAH	8 (3.2%)
Unilateral or bilateral SO	29 (11.6%)
TAH with Unilateral or bilateral SO	51 (20.4%)
Surgical staging	140 (56%)
Anesthesia type (%)	
General anesthesia (GA)	223 (89.2%)
Regional Anastasia (RA)	3 (1.2%)
Combined GA and RA	24 (9.6%)
Incision	
Midline	221 (88.4%)
Pfannenstiel	26 (10.4%)
Maylard	3 (1.2%)
Other organ resection	7 (2.8%)
Small bowel	5 (2%)
Colo-rectum	2 (0.8%)
Intraoperative other organ injuries	18 (7.2%)
Major Vessel	6 (2.4%)
Bowel	9 (3.6%)
Ureter	1 (0.4%)
Bladder	2 (0.8%)
Blood loss (ml)	median 300 (IQR 150-600)
Massive blood loss (> 1,500 ml)	7 (2.8%)
Operative time (min)	median 160 (IQR 110-240)

Table 2. Characteristic of patients (n = 250). (Cont.)

Complication	10 (4%)
Post-operative bleeding	2 (0.8%)
Bowel eviscerated	1 (0.4%)
Respiratory complication	4 (1.6%)
Femoral nerve neuropraxia	2 (0.8%)
Vagino-vesicle fistula	1 (0.4%)
Time to soft diet (days)	
Pain control	
Patient controlled analgesia (PCA)	26 (10.4%)
Conventional as-need analgesia	224 (89.6%)
Overall morphine dose (mg)	Mean 5.6 (SD ± 4)
Length of stay (days)	Median = 3 (IQR 3-4) (min 1 - max 13)
	Mean 3.5 (SD ± 1.4)
Length of stay > 3 days	140 (56%)
Cause of prolong LOS	98 (39.2%)
Patient preference	16 (6.4%)
Poor intake	15 (6%)
Poor ambulation	11 (4.4%)
Respiratory complication	
Re-operation	8 (3.2%)
Foley catheter related	29 (11.6%)
Fever	51 (20.4%)
Other	140 (56%)
Re-admission within 30 days	1 (0.4%)

CIS: carcinoma in situ, RHND: radical hysterectomy with pelvic node dissection, GA: general anesthesia, RA: regional anastasia, PCA: patient controlled analgesia, LOS: length of stay, IQR: interquartile range

The patients had an average length of post-operative hospital stay at 3.5 days and the median at 3 days with 164 (65.6%) patients who demonstrated good functional recovery and have 3 or less days, they were allocated to NLOS group and 86 (34.4%) patients who had more than 3 days of post-operative hospital stay, were allocated to PLOS group. The reasons of prolong hospital stay were poor oral intake (18 cases, 7.2%), poor ambulation (15 cases, 6%), Foley's catheter related condition (12 cases, 4.8%), respiratory complications (4 cases, 1.6%), fever (3 cases, 1.2%), reoperation (3 cases, 1.2%), other (7 cases, 2.8%) and 24 patients (9.6%) who met discharge criteria but preferred to stay in the hospital.

The present study found PLOS group had statistically significant ($p < 0.05$) association with more BMI, high ASA classification (ASA class 3, OR 2.74, 95%CI 1.17-6.25), disease of cervix (OR 2.16, 95%CI 1.04-4.35), radical hysterectomy with pelvic dissection operation (OR 6.01 95%CI 2.26-16.03), blood loss, prolong operation and complications (Table 3).

Table 3. Characteristic of patients by length of stay (LOS) and univariate analysis of risk factors associated with prolonged LOS.

	NLOS (n = 164)	PLOS (n = 86)	p value	OR (95%CI)
Age (years) mean ± SD	48.6 ± 12	50.7 ± 12.4	0.87	1.009 (0.986-1.032)
BMI (kg/m^2) mean ± SD	24.5 ± 4.4	25.9 ± 6.2	< 0.01	1.034 (0.980-1.091)
Underlying disease				
No underlying disease	106 (64.6%)	55 (63.9%)	0.77	0.94 (0.62-1.32)
Hypertension	39 (23.7%)	26 (30%)	0.26	1.33 (0.76-2.45)
Diabetes mellitus	19 (11.5%)	8 (9.3%)	0.58	0.78 (0.39-1.82)
Pulmonary disease	7 (4.2%)	2 (2.2%)	0.43	0.50 (0.12-2.60)
Other cancer	4 (2.4%)	0 (0%)	0.14	-
Other disease	5 (3%)	4 (4.6%)	0.51	1.55 (0.46-5.93)
ASA Classification			0.04	
1	54 (32.9%)	29 (33.7%)		1.01 (0.5-1.8)
2	99 (60%)	43 (50%)		0.63 (0.3-1.1)
3	11 (6.7%)	14 (16.2%)		2.74 (1.17-6.25)
Disease			< 0.01	
Ovarian neoplasm	80 (48.7%)	32 (37.2%)		0.62 (0.36-1.01)
Uterus neoplasm	65 (39.6%)	35 (40.6%)		1.04 (0.62-1.77)
Cervix neoplasm	19 (11.5%)	19 (22.0%)		2.16 (1.04-4.35)
Pathology			< 0.01	
Benign	77 (46.9%)	21 (24.4%)		0.36 (0.23-0.67)
Borderline or CIS	7 (4.2%)	5 (5.8%)		1.38 (0.42-4.49)
Malignant	80 (48.7%)	60 (69%)		2.42 (1.39-4.21)
Operation			< 0.01	
TAH	8 (4.8%)	0 (0%)		-
Unilateral or bilateral SO	25 (15.2%)	4 (4.6%)		0.27 (0.09-0.80)
TAH with Unilateral or bilateral SO	38 (23.1%)	13 (15.1%)		0.59 (0.29-1.18)
Surgical staging	87 (53%)	53 (61.6%)		1.42 (0.83-2.41)
RHND	6 (3.6%)	16 (18.6%)		6.01 (2.26-16.03)
Anesthesia type (%)			0.23	
General anesthesia (GA)	150 (91%)	73 (84%)		0.52 (0.23-1.17)
Regional Anastasia (RA)	2 (1.2%)	1 (1.1%)		0.95 (0.08-10.66)
Combined GA and RA	12 (7.3%)	12 (13.9%)		2.05 (0.88-4.79)
Other organ resections	3 (1.8%)	4 (4.6%)	0.14	2.66 (0.57-11.97)
Injuries	9 (5.4%)	9 (10.4%)	0.27	2.01 (0.76-5.27)
Blood loss (ml) median (IQR)	200 (100-450)	350 (300-850)	< 0.01	1.000 (1.000-1.010)
Operative time (min) median (IQR)	140 (100-200)	210 (150-300)	< 0.01	1.006 (1.003-1.010)
Complication	0 (0%)	10 (11.6%)	< 0.01	-
PCA	13 (7.9%)	13 (15.1%)	0.21	2.06 (0.91-4.68)
Morphine (mg) mean ± SD	5.3 (SD ± 4.5)	6.6 (SD ± 3.7)	0.77	1.13 (9.94-1.23)

CIS: carcinoma in situ, RHND: radical hysterectomy with pelvic node dissection, GA: general anesthesia, RA: regional anastasia, PCA: patient controlled analgesia, IQR: interquartile range

Discussion

In Thailand, the studies on ERAS care guidelines on gynecological surgery are currently limited especially in cancer surgery. In this study, we collected the data of the patient who underwent elective major gynecologic surgery which mostly were diagnosed or clinical suspected of malignant. We demonstrated good post-operative recovery with median postoperative hospital stay at 3 days and 65.6% of patients have 3 days or less which was consistent with most retrospective studies established in Gynecologic Oncology[8, 12-14].

Overall post-operative morphine dosage was low in this study (average 5.6 mg) due to our multimodality analgesia. PCA may be not suitable in our patient because low morphine needed and trended to associate with prolong hospital stay (15.1% vs 7.9%) but no statistical significant ($p = 0.21$).

This study demonstrated safety in our protocol with lower morbidity and mortality than most previous studies but may be due to patient selection bias[8, 12-15]. We found that more BMI, high ASA classification, disease of cervix, RHND operation, blood loss, prolong operation and complications are associated with PLOS that mostly were non-modifiable risk factors.

Many previous studies showed better results than ours with median post-operative hospital stay at 1 or 2 days and we had a lot of rooms to improve our protocol. First, no patient in this study underwent laparoscopic surgery which previous study demonstrated improvement post-operative recovery and shortened hospital stay[16]. Second, there were 24 patients in this study (9.6%) who met discharge criteria but preferred to stay in the hospital, indicated inadequate pre-operative counselling. Lastly, most patient with cervical cancer who underwent RHND (72%) had prolong hospital stay due to urinary retentions. Nerve sparing RHND has reported to improved bladder function[17, 18], this technique should be considered in selected patients.

However, there were several limitations to this study. First, there were a large amount of selection bias due to it was designed as a retrospective descriptive study and Surathani cancer hospital does not have Intensive Care Unit (ICU) and internal medicine staff, so we can not perform operation in high-risk patients and 8 patients who needed ICU or internal medicine care were referred to tertiary care hospital. Second, we did not have the result of the period before conducting ERAS protocol to compare because Gynecologic division in our hospital just opened in 2016. Lastly, our protocol was not strict, therefore the management was based on each surgeon's preference and this study did not evaluate the adherence of the patient to the protocol.

The ERAS program will help the hospital with earlier discharge, reduced costs of medical treatment, and reduced overcrowding problems but the program is still underused in gynecologic surgery. This study was a pilot study for our ERAS program, which was easily applied and showed a favorable outcome. In the future, we can use this result to improve our ERAS program for the benefit of the patients and the hospital.

Conclusion

Our ERAS program showed some potentials of patient care in major gynecologic surgery with median post-operative length of stay at 3 days and low complication rate. High BMI, high ASA classification, disease of cervix, RHND operation, blood loss, prolong operation and complications were associated with PLOS that mostly were non-modifiable risk factors. This result will be used to improve our ERAS program and promote the ERAS program in major gynecologic surgery.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence and Predictive Factors for Being High-risk of Obstructive Sleep Apnea Using Berlin Questionnaire in Polycystic Ovary Syndrome: Age - and BMI-matched study

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ABSTRACT

Objectives: To evaluate prevalence and predictive factors for being high-risk of obstructive sleep apnea (OSA) in women with and without polycystic ovary syndrome (PCOS).

Materials and Methods: This age and body mass index matched cross-sectional study recruited 94 women with ages between 20 and 40 years. Risk of OSA was assessed by Berlin questionnaire in 47 women with PCOS diagnosed by the Rotterdam criteria and 47 women without PCOS.

Results: Women with PCOS had significantly greater waist circumference, waist-hip ratio, hyperandrogenism (HA), biochemical and clinical HA, and poorer metabolic parameters, that is, total cholesterol, low-density lipoprotein cholesterol and insulin, compared to women without PCOS. Women with PCOS revealed a statistically significantly higher prevalence in being high-risk of OSA than women without PCOS (27.7% vs 6.4%, $p = 0.006$). Impaired fasting glucose (IFG, fasting plasma glucose ≥ 100 mg/dL) was an independent predictor of high-risk for OSA using Berlin questionnaire with an odds ratio (95% confidence interval) of 29.19 (1.26-674.04).

Conclusion: The prevalence of being high-risk of OSA assessed by Berlin questionnaire was higher in women with PCOS than those without PCOS. IFG but not PCOS was a significant key predictive factor associated with the development of being high-risk of OSA. Consequently, we suggested OSA risk screening using Berlin questionnaire should be assessed in women with PCOS. Polysomnography should be offered to the patients who either are being high-risk of OSA identified by questionnaire screening tool or having insulin resistance.

Keywords: obstructive sleep apnea syndrome, questionnaire, polycystic ovary syndrome, impaired fasting glucose.

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ความชุกและปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ โดยใช้แบบสอบถามเบอร์ลินในกลุ่มอาการถุงน้ำรังไข่หลายใบ: การศึกษาแบบเข้าคู่กันของอายุและค่าดัชนีมวลกาย

ณัฐณิชา กังวลกิจ, อารีย์พรรณ โสภณสฤษฏ์สุข, วิสาข์สิริ ตันตระกูลม, ชื่นกมล ชรากร, สิริลักษณ์ ตันธนาวิภาส

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ และหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวางแบบเข้าคู่กันของอายุและค่าดัชนีมวลกาย รวบรวมผู้เข้าร่วมวิจัย 94 ราย อายุระหว่าง 20 - 40 ปี 47 ราย เป็นหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบที่ได้รับการวินิจฉัยด้วเกณฑ์ Rotterdam และ 47 ราย เป็นหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ผู้เข้าร่วมวิจัยได้ทำแบบสอบถามเบอร์ลินเพื่อประเมินความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ*

ผลการศึกษา: *หญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบมีความความชุกของความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับสูงกว่าหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 27.7 เปรียบเทียบกับ ร้อยละ 6.4, p = 0.006) ระดับน้ำตาลในเลือดสูงกว่าปกติ (ระดับน้ำตาลในเลือดหลังอดอาหาร ≥ 100 มิลลิกรัม/เดซิลิตร) เป็นปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ โดยมีอัตราส่วนออด (ช่วงความเชื่อมั่น ร้อยละ 95) 29.19 (1.26-674.04)*

สรุป: *ความชุกของความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับสูงขึ้นอย่างมีนัยสำคัญทางสถิติในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ดังนั้นแนะนำให้ใช้แบบสอบถามเบอร์ลินในการคัดกรองความเสี่ยงของโรคหยุดหายใจขณะนอนหลับในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ในกรณีที่คัดกรองพบว่ามีความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ หรือมีระดับน้ำตาลในเลือดสูงกว่าปกติ แนะนำให้ส่งตรวจการนอนหลับเพื่อวินิจฉัยโรคหยุดหายใจขณะนอนหลับต่อไป*

คำสำคัญ: *โรคหยุดหายใจขณะนอนหลับ, แบบสอบถาม, กลุ่มอาการถุงน้ำรังไข่หลายใบ, ระดับน้ำตาลในเลือดสูงกว่าปกติ*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in almost 10% of reproductive-age women[1, 2]. The characteristics of PCOS include anovulation, hyperandrogenism (HA), insulin resistance (IR), and polycystic ovarian morphology assessed by ultrasonography. Multiple comorbidities of PCOS include IR, diabetes mellitus (DM), metabolic syndrome (MetS), obesity, non-alcoholic fatty liver disease, cardiovascular disease, depression, and sleep disorder[3, 4].

The most common sleep-related breathing disorder is obstructive sleep apnea (OSA). It is characterized by repeated episodes of breathing cessation during sleep[5]. The diagnosis of OSA is done by monitoring breathing during sleep. In-laboratory polysomnography (PSG) is the gold standard for the OSA diagnosis. However, the high cost and lack of availability of PSG are the main problems for investigating the patients suspected of having OSA[6]. Using some questionnaires i.e. Berlin and the STOP-BANG were the effective screening tools to identification of OSA patients[7].

OSA is an obesity-related condition[8]. Women with PCOS are frequently associated with the development of obesity[9]. Hence, it is not surprising that the prevalence of OSA is increased in women with PCOS[10, 11]. It is questionable that an increase of OSA in women with PCOS was related to either obesity or other associated conditions. The common co-exist mechanisms of PCOS and OSA such as obesity, IR, and HA might play a role in its etiology and contribute to the comorbidities of the other[12]. Moreover, the similar consequences of OSA and PCOS including metabolic and hormonal abnormalities might lead to more severe phenotypes of PCOS among women with OSA[13].

A recent systematic review and meta-analysis revealed that 35% of women with PCOS had OSA (95% confidence interval (CI) 22.2-48.9%)[11]; however, no study was ever performed in Thai PCOS patients. In the present study, the Berlin questionnaire was used for early identification OSA in PCOS women. The prevalence and predictive factors for being high risk of OSA in women with PCOS were investigated. We hypothesized that Thai women with PCOS have an increased risk of OSA when compared to Thai women without PCOS.

Materials and Methods

Between September 2020 and October 2021, 94 women ages 20 - 40 years were recruited in this present age and BMI matched cross-sectional study after written informed consent. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital (MURA2020/1023).

Forty-seven women with PCOS were recruited from the Endocrine Clinic, Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The inclusions criteria in PCOS group were: 1) women with PCOS diagnosed by Rotterdam criteria (which defined as two or more of the following three symptoms: anovulation, HA, or polycystic ovary[14]), and 2) no underlying disease associated with sleep disturbance such as depression, mood disorder, psychiatric disorder, severe chronic disease, malignancy, etc.

The control group was 47 women without PCOS who were recruited from local advertisements. The inclusion criteria for control women were: 1) having regular menstruation with menstrual duration between from 21 to 35 days, 2) no evidence of clinical or biochemical HA, and 3) no underlying disease associated with sleep disturbance such as depression, mood disorder, psychiatric disorder, severe chronic disease, malignancy, etc.

The exclusion criteria in both groups were other conditions related to sleep disorder including smoking, alcohol or caffeine drinking, sedative drug use, and receiving any medication with a side effect of drowsiness. None of the participants had received any hormonal contraceptive for at least 3 months.

The age of patients was categorized into 20 to 30 years and more than 30 to 40 years. The body mass index (BMI) was divided into less than 25 kg/m^2 and 25 kg/m^2 or more. After that, we matched the women with PCOS with the others in the control group one to one based on their ages and BMI.

All participants underwent a medical and past history interview, physical examination seeking for signs of HA and IR, laboratory investigation, and ultimately completing the

sleep disorder questionnaire.

Anthropometric Measurement

Weight, height, waist circumference (WC), and hip circumference were measured by the single investigator. WC was measured by a stretch-resistant tape at a midpoint between the lower margin of the lowest palpable rib and the iliac crest. Hip circumference was measured parallel to the floor around the widest part of the buttocks[15]. Waist-hip ratio (WHR) was defined as WC divided by the hip circumference. Weight in kilograms divided by the square of height on meters was considered for BMI.

Laboratory Methods

Blood was collected from all participants after fasting, at 8 o'clock, and evaluated for thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total testosterone (T), sex hormone-binding globulin (SHBG), fasting plasma glucose (FPG) and insulin. The second plasma samples for plasma glucose were assessed after 2 hours post- 75 g glucose-load (2h-PG). T and SHBG were performed by chemiluminescence assays (Immulite 2000 xpi, Siemens Healthineers Headquarters, Germany).

T (ng/mL) x 3.47 x 100 /SHBG (nmol/L) was the formula of the free androgen index (FAI) calculation. The homeostasis model assessment of IR (HOMA-IR) method was considered by the formula: HOMA-IR = insulin (μU/mL) × glucose (mg/dL)/405.

Sleep disorder questionnaire

All participants completed validated Thai versions of self-administered Berlin questionnaire (BQ)[16], Epworth sleepiness scale (ESS)[17], and Pittsburgh Sleep Quality Index (PSQI)[18] for assessing the risk of OSA, daytime sleepiness, and sleep disorder-breathing condition, respectively. All participants took the questionnaires in private room at the same visit when they recruited into this study. Five minutes were required for each questionnaire.

BQ was a survey screening the high risk of OSA with a sensitivity of 86% and specificity of 77% compared to apnea-hypopnea index (AHI) > 5 cut-off performed by polysomnography[19]. It consisted of 10 questions which were divided into 3 domains of sleep problems: 1) snoring behavior, 2) daytime sleepiness, and 3) hypertension or BMI > 30 kg/m^2. The positive score on the first and the second domain was considered when the symptoms occurred 3-4 times/week or more. The presence of hypertension or BMI > 30 kg/m^2 in the third domain was interpreted as the positive score. The positive score on 2 or more domains was diagnosed for being high-risk of OSA.

ESS was assessed for the degree of daytime sleepiness from 8 questions. The score ranged from 0-3 in each item. More than 10 scores were indicated for excessive daytime sleepiness.

PSQI was performed for overall sleep quality assessment over a 1-month time interval. It consisted of 7 aspects from 19 questions: 1) subjective sleep patients' quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbance, 6) use of sleep medication, and 7) daytime dysfunction. Each question yielded a score ranging from 0-3. More than 5 scores were considered as poor sleep quality.

Definition

A WC ≥ 80 cm and BMI ≥ 25.0 kg/m^2 were defined as abdominal obesity and obesity, respectively. MetS was diagnosed by 3 or more of the following criteria: 1) WC ≥ 80 cm, 2) TG ≥ 150 mg/dL, 3) HDL-C < 50 mg/dL, 4) Blood pressure ≥ 130/85 mmHg, and 5) FPG ≥ 100 mg/dL[20]. Biochemical HA was defined as FAI > 6.8[21] whereas clinical HA was characterized by acne, alopecia, and/or hirsutism[14]. HA was characterized by biochemical and/or clinical HA.

Level of FPG ≥ 100 mg/dL and 2-h PG during 75g-OGTT from 140 to 199 mg/dL were the criteria for the diagnoses of IFG and impaired glucose tolerance (IGT), respectively[22]. Homeostasis model assessment of IR (HOMA-IR) > 2.77 was defined as IR[23].

Sample size

Based on results from the study conducted by Babak et al, the prevalence of being high-risk of OSA was 47% and 15% in women with PCOS and without PCOS, respectively l[24]. These results were used for sample size calculation by two independent proportions at 95%CI (α =

0.05) and 90% power ($\beta = 0.1$). The sample size was 42 participants per group. The total sample size was 94 participants after adding 10% sample loss. There were 47 participants for each group.

Statistical Analysis

Statistical analyses were performed using SPSS program version 22 for Windows. T-test and chi-square test were analyzed for the normally distributed continuous and discrete data, respectively. Mann-Whitney U test was performed for non-normal distributed continuous data. Independent association of being high-risk of OSA was assessed by logistic regression. Univariate logistic regression was used for all participants. Mixed effects logistic regression model was performed for statistically significant factors in the univariate analyses. Odds ratio (OR) with 95%CI for the logistic regression was calculated. In all analyses, $p < 0.05$ was indicated statistically significant.

Results

There was no significant difference in several parameters between women with and without PCOS (median age 27 vs 27 years, $p = 0.423$ and median BMI 26.1 vs 25.1 kg/m^2, $p = 0.404$). WC and WHR were significantly increased in women with PCOS compared to women without PCOS; even though, the BMI was similar (WC 85 vs 74 cm, $p = 0.032$ and WHR 0.84 vs 0.79, $p < 0.001$). Women with PCOS had higher biochemical HA levels (T 42.0 vs 32.0 ng/ml, $p < 0.001$; SHBG 23.6 vs 45.2 nmol/L, $p = 0.012$ and FAI 5.95 vs 2.59, $p < 0.001$). More number of women had clinical HA and HA than those without PCOS, 29.8% vs 0%, $p < 0.001$ and 38.3% vs 4.3%, $p < 0.001$, respectively. Furthermore, metabolic parameters including circulatory TC, LDL, and insulin were higher in women with PCOS than those without PCOS, 207.0 vs 193.1 mg/dL $p = 0.030$, 138.5 vs 122.3 mg/dL $p = 0.024$, and 9.0 vs 7.7 µU/mL $p = 0.045$, respectively (Table 1).

Table 1. Baseline characteristics of PCOS and women without PCOS.

Characteristics	PCOS (n = 47)	without PCOS (n = 47)	p value
Age (years)	27.0 [24.0,30.0]	27.0 [24.0,32.0]	0.611
BMI (kg/m^2)	26.1 [20.9,31.2]	25.1 [19.5,27.8]	0.151
WC (cm)	85.0 [74.0,97.0]	74.0 [69.0,91.0]	0.019
HC (cm)	101.4 ± 11.5	100.1 ± 14.3	0.354
WHR	0.84 ± 0.06	0.79 ± 0.06	< 0.001
SBP (mmHg)	117.0 [111.0,121.0]	115.0 [108.0,125.0]	0.433
DBP (mmHg)	74.9 ± 9.2	75.7 ± 7.7	0.580
TSH (µU/mL)	1.39 [0.95,2.32[	1.86 [1.39,2.51]	0.052
FSH (µU/mL)	4.92 [3.97,5.63]	4.50 [2.93,5.73]	0.216
TG (mg/dL)	84.0 [63.0,125.0]	66.0 [52.0,103.0]	0.058
TC (mg/dL)	207.0 ± 33.2	193.1 ± 36.6	0.030
HDL-C (mg/dL)	54.3 ± 14.7	58.7 ± 14.3	0.142
LDL-C (mg/dL)	138.5 ± 35.6	122.3 ± 39.9	0.024
T (ng/mL)	42.0 [38.0,58.0]	32.0 [26.0,42.0]	< 0.001
SHBG (nmol/L)	23.6 [17.0,50.5]	45.2 [27.2,60.0]	0.001
FAI	5.95 [2.94,10.19]	2.59 [1.70,3.97]	< 0.001
Clinical HA	28 (29.8)	0 (0)	< 0.001
HA	36 (38.3)	4 (4.3)	< 0.001
FBG (mg/dL)	85.0 [78.0,89.0]	83.0 [78.0,88.0]	0.812
Insulin (µU/mL)	9.0 [7.6,14.3]	7.7 [5.8,10.1]	0.045
HOMA-IR	1.93 [1.33,3.10]	1.65 [1.25,2.34]	0.111
IR	15 (16)	8 (8.5)	0.093
MetS	10 (10.6)	8 (8.5)	0.600
ESS score	7.0 [6.0,11.0]	8.0 [5.0,10.0]	0.276
PSQI score	6.0 [4.0,9.0]	6.0 [4.0,7.0]	0.077

PCOS: polycystic ovary syndrome, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, TSH: thyroid stimulating hormone, FSH: follicle-stimulating hormone, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T: total testosterone, SHBG: sex hormone-binding globulin, FAI: free androgen index, HA: hyperandrogenism, FPG: fasting plasma glucose, 2hr-PP glucose: 2 hour postprandial glucose, HOMA-IR: homeostatic model assessment of insulin resistance, MetS: metabolic syndrome, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index. Data are presented as median [25th, 75th percentile] or mean ± SD or n (%) as appropriate.

The prevalence of being high-risk of OSA among women with PCOS was 27.7% compared to 6.4% in women without PCOS (p = 0.006). Nevertheless, there were no statistical differences in the number of participants with excessive daytime sleepiness assessed by ESS (PCOS vs without PCOS, 31.1 vs 21.3%, p = 0.243) and poor sleep quality assessed by PSQI (PCOS vs without PCOS, 59.6% vs 53.2%, p = 0.555), respectively (Table 2).

Baseline characteristics comparing between women with high- and low-risk of OSA were shown in Table 3.

Table 2. The prevalence of being high-risk of OSA based on Berlin questionnaire and sleep disorder assessment in women with PCOS comparing to women without PCOS.

Sleep disorder assessment	PCOS (n = 47) n (%)	Without PCOS (n = 47) n (%)	p value
Being high-risk OSA (Berlin questionnaire)	13 (27.7)	3 (6.7)	0.006
Excessive daytime sleepiness (ESS, score > 10)	15 (31.9)	10 (21.3)	0.243
Poor sleep quality (PSQI, score > 5)	28 (59.6)	25 (53.2)	0.533

PCOS: polycystic ovary syndrome, ESS: Epworth sleepiness scale, PSQI: Pittsburgh Sleep Quality Index

Table 3. Baseline characteristics of being high- and low-risk of OSA based on Berlin questionnaire.

Characteristics	Being high-risk OSA (n = 16)	Being low-risk OSA (n = 78)	p value
Age (years)	29.0 [24.8,33.0]	26.5 [24,30]	0.111
BMI (kg/m^2)	33.4 [28.4,36.2]	23.3 [19.8,28.0]	< 0.001
WC (cm)	98.5 [91.5,108.5]	74.0 [69.0,86.3]	< 0.001
HC (cm)	111.6 ± 9.9	98.5 ± 12.4	< 0.001
WHR	0.88 ± 0.06	0.80 ± 0.06	< 0.001
SBP (mmHg)	121.5 [111.8,126.0]	115.5 [110.0,121.3]	0.056
DBP (mmHg)	80.3 ± 8.3	74.3 ± 8.2	0.009
TSH (μU/mL)	1.39 [1.13,2.11]	1.69 [1.17,2.48]	0.457
FSH (μU/mL)	5.18 [4.27,5.51]	4.44 [3.31,5.74]	0.629
TG (mg/dL)	123.0 [70.8,199.8]	73.0 [54.0,98.5]	0.009
TC (mg/dL)	205.7 ± 22.4	198.9 ± 37.6	0.526
HDL-C (mg/dL)	47.8 ± 13.3	58.3 ± 14.2	0.009
LDL-C (mg/dL)	144.0 ±27.6	128.0 ±39.9	0.048
T (ng/mL)	39.0 [28.0,46.3]	39.5 [29.8,53.0]	0.710
SHBG (nmol/L)	20.2 [14.2,32.0]	41.0 [23.3,59.2]	0.001
FAI	6.52 [4.40,9.90]	3.08 [1.91,5.96]	0.009
Clinical HA	11 (11.7)	17 (18.1)	< 0.001
HA	12 (12.8)	28 (29.8)	0.004
FBG (mg/dL)	88.5 [85.0,100.8]	82.5 [78.0,87.3]	0.004
2hr-PP Glucose (mg/dL)	114.5 [102.8,169.8]	92.5 [77.0,113.0]	0.005
Insulin (μU/mL)	12.7 [9.0,19.8]	8.4 [6.0,10.3]	0.001
HOMA-IR	3.09 [2.02,4.29]	1.71 [1.23,2.33]	< 0.001
MetS	8 (8.5)	10 (10.6)	0.001
PCOS	13 (13.8)	34 (36.2)	0.006
ESS score	10.5 [6.0,12.0]	7.0 [5.8,10.0]	0.126
PSQI score	8.5 [6.0,10.8]	5.5 [4.0,7.0]	0.013

PCOS: polycystic ovary syndrome, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, TSH: thyroid stimulating hormone, FSH: follicle-stimulating hormone, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T: total testosterone, SHBG: sex hormone-binding globulin, FAI: free androgen index, HA: hyperandrogenism, FPG: fasting plasma glucose, 2hr-PP glucose: 2 hour postprandial glucose, HOMA-IR: homeostatic model assessment of insulin resistance, MetS: metabolic syndrome, PCOS: polycystic ovary syndrome, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index.

BMI, WC, HC, WHR, DBP, TG, LDL-C, FAI, clinical HA, HA, FPG, 2hr-PP glucose, insulin, HOMA-IR, MetS, PCOS, and PSQI score were significantly higher while HDL-C and SHBG were lower in women with high risk of OSA than in women with low risk of OSA. Additionally, there were higher number of participants with excessive daytime sleepiness and poor sleep quality in high risk of OSA than low risk OSA groups, 50% vs 21.8%, p = 0.030 and 81.2% vs 51.5%, p = 0.030, respectively (Table 4).

Table 4. Score of Berlin questionnaire, Epworth sleepiness scale, and Pittsburgh Sleep Quality Index.

Sleep disorder assessment	PCOS (n = 47) median [25th, 75th percentile] or n (%)	Without PCOS (n = 47) median [25th, 75th percentile] or n (%)	p value	Being high-risk of OSA (n = 16) median [25th, 75th percentile] or n (%)	Being low-risk of OSA (n = 78) median [25th, 75th percentile] or n (%)	p value
BQ						
low-risk	34 (72.3)	44 (93.3)	-	-	-	-
high-risk	13 (27.7)	3 (6.7)	0.006	-	-	-
ESS						
Score	7.0 [6.0,11.0]	8.0 [5.0,10.0]	0.276	10.5 [6.0,12.0]	7.0 [5.8,10.0]	0.126
≤ 10	32 (68.1)	37 (78.7)	-	8 (50.0)	61 (78.2)	-
> 10	15 (31.9)	10 (21.3)	0.243	8 (50.0)	17 (21.8)	0.030
PSQI						
Score	6.0 [4.0,9.0]	6.0 [4.0,7.0]	0.077	8.5 [6.0,10.8]	5.5 [4.0,7.0]	0.013
≤ 5	21 (40.4)	22 (46.8)	-	3 (18.8)	38 (48.7)	-
> 5	28 (59.6)	25 (53.2)	0.533	13 (81.2)	40 (51.3)	0.030

PCOS: polycystic ovary syndrome, OSA: obstructive sleep apnea, BQ: berlin questionnaire, ESS: epworth sleepiness scale, PSQI: pittsburgh sleep quality index. Excessive daytime sleepiness defined as ESS > 10. Poor sleep quality defined as PSQI > 5

Univariate binary logistic regression showed that being high-risk of OSA was significantly associated with obesity (BMI ≥ 25 kg/m^2), central obesity (WC ≥ 80 cm), WHR ≥ 0.8, HDL-C < 50 mg/dL, clinical HA, HA, IFG (FPG ≥ 100 mg/dL), IR (HOMA-IR > 2.77), MetS, and PCOS. These factors were entered into mixed effects logistic regression model and demonstrated that the independent predictor of being high-risk of OSA using BQ was IFG with an odds ratio (95%CI) of 29.19 (1.26-674.04). Interestingly, we found no significant effects of PCOS on being high-risk of OSA. (Table 5)

Table 5. Risk factors associated with being high-risk of OSA based on Berlin questionnaire in women with and without PCOS.

Variables	Univariate			Multivariate		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
BMI ≥ 25 kg/m2	9.06	1.93-42.58	0.005			
WC ≥ 80 cm	10.06	2.14-47.35	0.003			
WHR ≥ 0.8	7.00	1.49-32.87	0.014			
HDL-C < 50 mg/dL	3.27	1.09-9.87	0.035			
Clinical HA	7.89	2.41-25.84	0.001			
HA	5.36	1.58-18.19	0.007			
FPG ≥ 100 mg/dL	11.36	2.38-54.35	0.002	29.19	1.26-674.04	0.035
HOMA-IR > 2.77	8.33	2.58-26.97	< 0.001			
MetS	6.80	2.08-22.21	0.002			
PCOS	5.61	1.48-21.26	0.011			

PCOS: polycystic ovary syndrome, OSA: obstructive sleep apnea, BQ: berlin questionnaire, ESS: epworth sleepiness scale, PSQI: pittsburgh sleep quality index. Excessive daytime sleepiness defined as ESS > 10. Poor sleep quality defined as PSQI > 5

Discussion

The present study demonstrated that the prevalence of being high-risk of OSA was statistically significantly increased among women with PCOS compared to women without PCOS (27.7% vs 6.4%, p = 0.006). PCOS was not the risk factor associated with the presence of being high-risk of OSA but the IFG, a comorbidity of PCOS, was a significant predictive factor of being high-risk of OSA assessed by BQ with an odds ratio (95%CI) of 29.19 (1.26-674.04). Women with high risk of OSA had poorer metabolic parameters and higher number of excessive daytime sleepiness and poor sleep quality than those with low risk of OSA.

Data from the present study confirmed that women with PCOS had the increased prevalence of being high-risk of OSA assessed by BQ compared to women without PCOS irrespective of obesity (27.7% vs 6.4%, p = 0.006). The results were compatible with the studies conducted by Mokhlesi et al[24], Hachul et al[25], and Melike Demir Çaltekin et al[26]. The increased development of OSA in women with PCOS was further supported by various studies diagnosed by polysomnography[10, 11].

The present study found that IFG was an important risk factor of being high-risk of OSA. The main pathophysiology of OSA includes intermittent hypoxia and sleep fragmentation. Patients with OSA were exposed to chronic intermittent hypoxia which led to down-regulation of insulin receptors and inhibition of the insulin signaling pathway. All of these alterations contributed to insulin resistance, hyperinsulinemia, and hyperglycemia[27]; therefore, this might explain why IFG was the important predictor of being high-risk of OSA. Likewise, previous studies from Seicean et al[28] and Kim et al[29] demonstrated that IFG was significantly associated with sleep-disorder breathing and OSA, respectively.

Although data from the present study suggested that surveillance for OSA should be offered to women with PCOS because of the higher number of OSA in women with PCOS than without PCOS, the high cost and the difficult accessibility of in-laboratory polysomnography would hinder OSA investigation for every PCOS women. Using screening tool to identify a high-risk patient for OSA or focusing on patients who have IR, a significant factor contributed to OSA, and then performed polysomnography in those women may be an alternative strategy to evaluate sleeping disorder. However, a comparison of OSA surveillance in every single PCOS women and women with a significant factor, IFG, or with high risk of OSA should be further studied.

Both excessive daytime sleepiness (EDS) and poor sleep quality (PSQ) are the detrimental clinical outcomes of OSA. EDS was serious risk factors of traffic accidents and decreased work performance. However, there was no significant difference of EDS between women with and without PCOS. These finding was compatible with Hachul et al's study[25]. Poor sleep quality using PSQI was demonstrated in 59.6% of women with PCOS that was paralleled with previous study from Melike Demir Çaltekin[26]. Nevertheless, the detection of poor sleep quality did not significantly different between women with and without PCOS in the present study. These finding was incompatible with study conducted by Hachul et al[25] and Melike Demir Çalteki et al[26]. Therefore, the present study revealed that PCOS was not only cause of EDS and PSQ. Poor sleep hygiene, sleep disorder, chronic health condition, and mental health condition might be the etiologies of EDS and PSQ. In contrast, there were higher number of participants with EDS and PSQ in high risk of OSA than low risk OSA groups. While only PCOS did not contribute to EDS and PSQ, being high-risk of OSA increased risk to EDS and PSQ. This result suggested the necessity of evaluation of OSA in women with PCOS.

The strength of the present study was that it was the first study in Thailand about being high-risk of OSA in women with PCOS. Additionally, we designed an age and BMI matched study to avoid confounding effects on OSA risk. Despite a cross-sectional study, the present study also had some limitations. Firstly, polysomnography was not performed. It is a gold standard for the diagnosis of OSA. Nevertheless, the

present study assessed OSA risk using a questionnaire that has a high positive and negative predictive value for the detection of OSA. Secondly, the small sample to evaluate the predictive factors for being high-risk of OSA might not show some significant factors.

Conclusion

The present study showed that the prevalence of being high-risk of OSA was significantly higher in women with PCOS than women without PCOS. PCOS was not a potential predictor of being high-risk of OSA but IFG, a comorbidity of PCOS, was the key predictive factor. Consequently, we suggested that OSA risk screening using Berlin questionnaire should be assessed in women with PCOS. Polysomnography should be evaluated in the patients who either are being high-risk of OSA identified by questionnaire screening tool or having IR. Women with high risk of OSA had poorer metabolic parameters and higher excessive daytime sleepiness and poor sleep quality than those with low risk OSA.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence of Gestational Diabetes Diagnosed before 24 Weeks of Gestation

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ABSTRACT

Objectives: To determine prevalence of gestational diabetes mellitus (GDM) diagnosed before 24 weeks of gestation (early GDM), to evaluate associated risk factors, and to compare pregnancy outcomes between different GDM status.

Materials and Methods: A total of 480 women who started antenatal care before 24 weeks of gestation were included. All women received a universal 2-step approach for GDM screening and diagnosis during first antenatal care visit and repeat at 24 - 28 weeks of gestation. Data were extracted from medical records, including baseline, obstetric and antenatal care data, GDM risks, diagnosis of GDM, and pregnancy outcomes. Prevalence of overall GDM, early and late GDM were estimated. Various characteristics and pregnancy outcomes were compared between women without GDM, early, and late GDM.

Results: Overall prevalence of GDM was 20%. Majority of GDM were diagnosed before 24 weeks of gestation (early GDM) with the prevalence of 14.4% which contributed to 71.9% of all GDM cases. Both early and late GDM were more likely to be overweight and have previous GDM. Early GDM significantly had lower gestational weight gain than those without GDM. Rates of large for gestational age (LGA) and macrosomia were slightly higher in GDM women than those without GDM. The only significant risk factor for early GDM was previous GDM with adjusted odds ratio 5.38, 95% confidence interval 1.16 - 24.92 (p = 0.031).

Conclusion: Prevalence of early GDM was 14.4% which contributed to 71.9% of all GDM cases. Pregnancy outcomes were not significantly different between early, late GDM and those without GDM. The only independent associated factor was previous GDM.

Keywords: gestational diabetes mellitus, early GDM, late GDM, risk factor, pregnancy outcomes.

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ความชุกของภาวะเบาหวานขณะตั้งครรภ์ที่ตรวจพบก่อน 24 สัปดาห์

กานต์กมล ประสิทธิ์, ดิฐกานต์ บริบูรณ์หิรัญสาร

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกของภาวะเบาหวานขณะตั้งครรภ์ที่ตรวจพบที่อายุครรภ์น้อยกว่า 24 สัปดาห์ และประเมินปัจจัยเสี่ยงที่เกี่ยวข้อง และเปรียบเทียบผลลัพธ์ของการตั้งครรภ์ระหว่างการตรวจพบเบาหวานในลักษณะต่างๆ*

วัสดุและวิธีการ: *เก็บข้อมูลจากสตรีตั้งครรภ์ที่มาฝากครรภ์ก่อน 24 สัปดาห์ จำนวน 480 ราย โดยทุกรายได้รับการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์ตามแนวทางของโรงพยาบาลศิริราช โดยตรวจเมื่อมาฝากครรภ์ครั้งแรกและที่อายุครรภ์ 24 - 28 สัปดาห์ รวบรวมข้อมูลจากบันทึกเวชระเบียน ประกอบด้วย ข้อมูลทั่วไป ข้อมูลทางสูติศาสตร์และการฝากครรภ์ ความเสี่ยงของภาวะเบาหวานขณะตั้งครรภ์ การวินิจฉัยภาวะเบาหวานขณะตั้งครรภ์ และผลลัพธ์ของการตั้งครรภ์ คำนวณหาความชุกของภาวะเบาหวานที่วินิจฉัยก่อนและหลัง 24 สัปดาห์ เปรียบเทียบข้อมูลต่างๆ และผลลัพธ์ของการตั้งครรภ์ระหว่างการตรวจพบเบาหวานในลักษณะต่างๆ*

ผลการศึกษา: *พบความชุกของภาวะเบาหวานในระหว่างตั้งครรภ์ร้อยละ 20 โดยร้อยละ 71.9 ตรวจพบก่อนอายุครรภ์ 24 สัปดาห์ หรือคิดเป็นร้อยละ 14.4 จากหญิงตั้งครรภ์ทั้งหมด กลุ่มที่ตรวจพบภาวะเบาหวานขณะตั้งครรภ์ทั้งก่อนและหลัง 24 สัปดาห์ มีน้ำหนักตัวที่เพิ่มขึ้นน้อยกว่ากลุ่มที่ไม่เป็นเบาหวานอย่างมีนัยสำคัญทางสถิติ และพบอัตราการเกิดทารกมีน้ำหนักตัวมากกว่าอายุครรภ์ และทารกที่มีน้ำหนักเกิน 4,000 กรัม สูงกว่ากลุ่มที่ไม่เป็นเบาหวานอย่างมีนัยสำคัญทางสถิติ ปัจจัยเสี่ยงที่สัมพันธ์กับภาวะเบาหวานในระหว่างการตั้งครรภ์ที่ตรวจพบก่อน 24 สัปดาห์ ได้แก่ การมีประวัติเบาหวานขณะตั้งครรภ์ในครรภ์ก่อน (adjusted odds ratio 5.38, 95% confidence interval 1.16 - 24.92, p = 0.031)*

สรุป: *ความชุกของภาวะเบาหวานขณะตั้งครรภ์ที่พบก่อนอายุครรภ์ 24 สัปดาห์เท่ากับร้อยละ 14 โดยคิดเป็นร้อยละ 71.9 ของภาวะเบาหวานขณะตั้งครรภ์ทั้งหมด ไม่พบความแตกต่างอย่างมีนัยสำคัญระหว่างผลลัพธ์ของการตั้งครรภ์ระหว่างการตรวจพบเบาหวานในลักษณะต่างๆ ปัจจัยเสี่ยงที่สัมพันธ์กับภาวะเบาหวานในระหว่างตั้งครรภ์ที่ตรวจพบก่อน 24 สัปดาห์ ได้แก่ การมีประวัติเบาหวานขณะตั้งครรภ์ในครรภ์ก่อน*

คำสำคัญ: *ภาวะเบาหวานขณะตั้งครรภ์, อายุครรภ์ที่วินิจฉัย, ปัจจัยเสี่ยง, ผลลัพธ์ของการตั้งครรภ์*

Introduction

Gestational diabetes mellitus (GDM) is a condition in which carbohydrate intolerance develops during pregnancy[1, 2], incidence of GDM has increased as a result of worldwide increase in overweight and obese women[1-3]. As previously reported in many studies, GDM has been associated with increased risk of maternal and neonatal morbidities, including large for gestational age (LGA) fetus or fetal macrosomia, cesarean delivery, birth injuries, preeclampsia, and future risk for diabetes mellitus[1-3].

A recent report from Siriraj Hospital, prevalence of GDM was 13.9% from a risk-based screening and, among which, 9.2% was diagnosed before 24 weeks of gestation, accounted for 65.9% of all GDM[4]. The results were similar to another study from the same institution that of 10.2% GDM prevalence, 5.3% of which was diagnosed before 20 weeks of gestation[5]. A systematic review reported that, among GDM, 15-70% can be detected early in pregnancy before 24 weeks of gestation, depending on the setting, criteria used and screening strategy[6].

GDM diagnosed early in pregnancy were reported to be at increased risk of adverse maternal and neonatal outcomes, including preeclampsia, insulin therapy, LGA, macrosomia, neonatal hypoglycemia, perinatal morbidities and mortality[6-13]. In a meta-analysis of 13 cohort studies, increased risk of perinatal mortality, neonatal hypoglycemia, and insulin use were observed, compared to late-onset GDM women, despite treatment[6]. However, factors associated with early GDM and the benefit of early treatment were still not clear.

After decades of risk-based GDM screening, a universal screening is currently adopted as an institutional guideline that all pregnant women are offered GDM screening during their first visit and repeat during 24 - 28 weeks of gestation. However, the prevalence of GDM as well as those diagnosed early in pregnancy have not been evaluated. Therefore, the objectives of this study were to determine prevalence of GDM diagnosed before 24 weeks of gestation (early GDM). In addition, associated risk factors were evaluated and pregnancy outcomes between different GDM status were compared.

Materials and Methods

The cross-sectional study was conducted in 480 pregnant women who received universal GDM screening at Siriraj Hospital after approval from Institutional Review Board. Women with singleton pregnancy who started antenatal care before 24 weeks of gestation were included, while those with pre-existing diabetes and those with severe fetal anomalies or fetal death were excluded. Sample size was calculated based on the prevalence of GDM diagnosed before 24 weeks of 10% from a pilot study. At 95% significance level and 3% acceptable error, at least 470 women are required, including 20% loss.

According to current institutional guideline, a universal 2-step approach is used for GDM screening and diagnosis to all pregnant women during first antenatal care visit. A 50-g glucose challenge test (GCT) is used as a screening test with 140 mg/dL cut-off value. A 100-g oral glucose tolerance test (OGTT) was used to diagnose GDM, using Carpenter and Coustan criteria. The tests are repeated during 24 - 28 weeks of gestation if initial tests were normal. After GDM diagnosis, dietary counseling and nutritional therapy were offered. A 2-hour postprandial plasma glucose was used to evaluate glycemic control during follow-up was by either intermittent test or self-monitoring with a glucose meter. Insulin therapy was initiated as necessary. GDM that is diagnosed before 24 weeks of gestation is considered “early GDM” and those diagnosed during 24 - 28 weeks are defined as “late GDM”.

Data were extracted from medical records, including baseline, obstetric and antenatal care data, GDM risks, diagnosis of GDM, and pregnancy outcomes. GDM risks included age ≥ 30 years, DM in family, body mass index (BMI) ≥ 25 kg/m^2, previous GDM, previous macrosomia, previous congenital anomaly or intrauterine fetal death, and hypertension. Pre-pregnancy BMI and gestational weight gain (GWG) were classified according to Institute of Medicine (IOM)

recommendation[14]. Data on pregnancy outcomes were collected, including delivery data, GWG, preeclampsia, birth weight, birth weight for gestational age, birth asphyxia, neonatal hypoglycemia, and neonatal intensive care unit (NICU) admission. Prevalence of overall GDM, early and late GDM were estimated. Various characteristics and pregnancy outcomes were compared between women without GDM, early, and late GDM.

Descriptive statistics were used to describe various characteristics, including mean, standard deviation, number, and percentages as appropriate. Chi-square test and one-way analysis of variance (ANOVA) with post-hoc comparison were used to compare characteristics between the 3 groups as appropriate. Logistic regression analysis was used to determine independent associated factors for early and late GDM, adjusted for potential confounders, including parity, age, BMI, previous GDM, and hypertension. A p value of < 0.05 was considered statistically significant.

Results

The study included 480 pregnant women who received early universal GDM screening and baseline characteristics are described in Table 1. Mean age was 30.4 years and 50.6% were nulliparous. Mean BMI was 22.8 kg/m^2, 17.7% were overweight and 7.9% were obese. Common GDM risk factors were age of ≥ 30 years (55%), BMI of ≥ 25 kg/m^2 (25%), and history of DM in first degree relatives (18.1%). While 31.5% of the women did not have any GDM risks, 40% had 1 risk and 28.5% had 2 or more risks.

Table 1. Baseline characteristics of the study population (n = 480).

Characteristics	
Mean age ± SD (years)	30.4 ± 5.9
Mean BMI ± SD (kg/m^2)	22.8 ± 4.6
Nulliparous, n (%)	243 (50.6)
BMI category, n (%)	
Normal (18.5-24.9 kg/m^2)	290 (60.4)
Underweight (< 18.5 kg/m^2)	67 (14)
Overweight (25-29.9 kg/m^2)	85 (17.7)
Obese (≥ 30 kg/m^2)	38 (7.9)
GDM risk factors, n (%)	
Age ≥ 30 years	264 (55)
DM family	87 (18.1)
BMI ≥ 25 kg/m^2	120 (25)
Previous GDM	10 (2.1)
Previous macrosomia	6 (1.3)
Previous anomaly/fetal death	12 (2.5)
Hypertension	5 (1)
Number of GDM risks, n (%)	
No risk	151 (31.5)
1	192 (40)
≥ 2	137 (28.5)

SD: standard deviation, BMI: body mass index, GDM: gestational diabetes

Table 2 shows characteristics of GDM diagnosis. Overall prevalence of GDM from early universal screening was 20%. Majority of GDM were diagnosed before 24 weeks of gestation (early GDM) with the

prevalence of 14.4% and mean GA at diagnosis of 10 weeks of gestation. Prevalence of late GDM, diagnosed after 24 weeks of gestation, was 5.6% with mean GA at diagnosis of 26.6 weeks of gestation. Early GDM contributed to 71.9% of all GDM cases. Of all GDM women, insulin use was required in 9.4%.

Various characteristics were compared between different GDM diagnosis and the results are shown in Table 3. While other characteristics were comparable between groups, BMI of ≥ 25 kg/m^2 and previous GDM were significantly more common in both early and late GDM than those without GDM (p = 0.029 and < 0.001, respectively).

Table 2. Diagnosis of GDM (n = 480).

Diagnosis of GDM	n (%)
No GDM	384 (80)
Early GDM	69 (14.4)
Mean GA at diagnosis ± SD (weeks)	10.0 ± 4.0
Late GDM	27 (5.6)
Mean GA at diagnosis ± SD (weeks)	26.6 ± 2.5

SD: standard deviation, GDM: gestational diabetes, GA: gestational age

Table 3. Comparison of characteristics between different GDM diagnosis.

Characteristics	No GDM (n = 384)	Early GDM (n = 69)	Late GDM (n = 27)	p value
Mean age ± SD (years)	30.2 ± 5.8	31.5 ± 5.3	32.3 ± 5.6	0.052[a]
Mean BMI ± SD (kg/m^2)	22.7 ± 4.6	23.1 ± 4.2	23.5 ± 4.0	0.600[a]
Nulliparous	181 (47.1%)	43 (62.3%)	13 (48.1%)	0.067[b]
BMI category				0.386[b]
Normal (18.5-24.9 kg/m^2)	225 (58.6%)	47 (68.1%)	18 (66.7%)	
Underweight (< 18.5 kg/m^2)	61 (15.9%)	4 (5.8%)	2 (7.4%)	
Overweight (25-29.9 kg/m^2)	67 (17.4%)	13 (18.8%)	5 (18.5%)	
Obese (≥ 30 kg/m^2)	31 (8.1%)	5 (7.2%)	2 (7.4%)	
GDM risk factors				
Age ≥ 30 years	203 (52.9%)	44 (63.8%)	17 (63%)	0.17[b]
DM family	96 (25%)	17 (24.6%)	7 (25.9%)	0.991[b]
BMI ≥ 25 kg/m^2	61 (15.9%)	20 (29%)	6 (22.2%)	0.029[b]
Previous GDM	3 (0.8%)	5 (7.2%)	2 (7.4%)	< 0.001[b]
Previous macrosomia	5 (1.3%)	1 (1.4%)	0 (0%)	0.83[b]
Previous anomaly	9 (2.3%)	1 (1.4%)	2 (7.4%)	0.221[b]
Hypertension	4 (1.0%)	1 (1.4%)	0 (0%)	0.821[b]
Number of GDM risks				0.119[b]
No risk	126 (32.8%)	18 (26.1%)	7 (25.9%)	
1	159 (41.4%)	23 (33.3%)	10 (37%)	
≥ 2	99 (25.8%)	28 (40.6%)	10 (37%)	

[a] Analysis of variance, [b] Chi-square

SD: standard deviation, BMI: body mass index, GDM: gestational diabetes

Table 4 shows comparison of pregnancy outcomes between different GDM diagnosis. GWG was significantly higher among those without GDM (p = 0.011), and post hoc analysis showed that early GDM significantly had lower GWG than those without GDM (11.9 vs. 14.1 kg, p = 0.011). In addition, early GDM also had significantly lower proportion of excessive weight gain than the other 2 groups (p = 0.03). Among GDM, insulin was required only among early GDM women (13%). Mean GA at delivery, route of delivery, mean birth weight, and preeclampsia were comparable between the 3 groups. However, it should be noted that LGA was slightly higher in GDM women than those without GDM (26.1% in early GDM, 29.6% in late GDM, and 18.8% in no GDM) but without statistical significance. Rates of macrosomia also increased among both early and late GDM but also without statistical significance (7.2% in early GDM, 7.4% in late GDM, and 2.1% in no GDM). Other neonatal outcomes were comparable between the 3 groups.

Table 4. Comparison of pregnancy outcomes between different GDM diagnosis.

Characteristics	No GDM (n = 384)	Early GDM (n = 69)	Late GDM (n = 27)	p value
Mean GA at delivery ± SD (weeks)	38.1 ± 1.3	37.8 ± 1.7	37.8 ± 1.8	0.182[a]
Mean gestational weight gain ± SD (kg)	14.1 ± 5.8	11.9 ± 5.9*	12.9 ± 5.7	0.011[a]
GWG category				0.03[b]
Normal	127 (33.1%)	26 (37.7%)	5 (18.5%)	
Less than recommendation	95 (24.7%)	25 (36.2%)	11 (40.7%)	
Excessive weight gain	162 (42.2%)	18 (26.1%)	11 (40.7%)	
Insulin use		9 (13%)	0 (0%)	0.057[b]
Route of delivery				0.485[b]
Vaginal delivery	220 (57.3%)	42 (60.9%)	13 (48.1%)	
Primary cesarean section	104 (27.1%)	13 (18.8%)	9 (33.3%)	
Repeat cesarean section	60 (15.6%)	14 (20.3%)	5 (18.5%)	
Birth weight ± SD (g)	3,067.0 ± 434.8	3,104.2 ± 562.7	3,227.4 ± 614.3	0.205[b]
Birth weight category				0.255[b]
AGA	291 (75.8%)	46 (66.7%)	19 (70.4%)	
SGA	21 (5.5%)	5 (7.2%)	0 (0%)	
LGA	72 (18.8%)	18 (26.1%)	8 (29.6%)	
Macrosomia	8 (2.1%)	5 (7.2%)	2 (7.4%)	0.032[b]
Preeclampsia	14 (3.6%)	4 (5.8%)	0 (0%)	0.394[b]
Apgar at 1 min < 7	14 (3.6%)	5 (7.2%)	1 (3.7%)	0.384[b]
Apgar at 5 min < 7	1 (0.3%)	0 (0%)	0 (0%)	0.882[b]
Phototherapy	60 (15.6%)	10 (14.5%)	4 (14.8%)	0.968[b]
Hypoglycemia	10 (2.6%)	5 (7.2%)	1 (3.7%)	0.141[b]
NICU admission	9 (2.3%)	3 (4.3%)	1 (3.7%)	0.607[b]

* Significant different from women without GDM, p = 0.01 [a] Analysis of variance, [b] Chi-square

SD: standard deviation, GA: gestational age, GDM: gestational diabetes, GWG: gestational weight gain, SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age, NICU: neonatal intensive care unit

Logistic regression analysis was performed to determine independent risk factors associated with early GDM and the results are shown in Table 5. After adjusting for potential confounders, the

only significant risk factor for early GDM was previous GDM with adjusted odds ratio (OR) 5.38, 95% confidence interval (CI) 1.16 - 24.92 (p = 0.031).

Table 5. Logistic regression analysis to determine independent risk of early GDM.

Risk factors	Adjusted OR	95%CI	p value
Nulliparous	1.55	0.89-2.69	0.12
Age ≥ 30 years	1.39	0.79-2.42	0.24
BMI ≥ 25 kg/m^2	0.8	0.43-1.50	0.501
Family history of DM	1.75	0.92-3.31	0.085
Previous GDM	5.38	1.16-24.92	0.031

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

Discussion

The results of this study showed that overall prevalence of GDM was 20% and prevalence of GDM diagnosed before 24 weeks of gestation (early GDM) was 14.4% with mean GA at diagnosis of as early as 10 weeks of gestation. The prevalence of both overall GDM and early GDM increased from previous reports from the same institution[4, 5]. This is due to the change in screening protocol from risk-based to universal screening protocol. Contribution of early GDM also increased from 50 - 65% to as many as 71.9% as shown in this study. Previous studies reported variations in prevalence of early GDM, ranging from 1-20% of all pregnant women[9, 10]. A systematic review also reported the prevalence of 15-70% of all GDM cases[6]. Differences of the results between studies were due to variations in study population as well as screening and diagnostic strategies and criteria in each setting.

In terms of risk factors for early GDM, the results showed that BMI of ≥ 25 kg/m^2 and previous GDM were significantly more common in early GDM than those without GDM in univariate analysis. However, after adjusting for potential confounders, the only significant risk factor for early GDM was previous GDM (adjusted OR 5.38, 95%CI 1.16 - 24.92, p = 0.031). Previous GDM was an important risk for GDM in subsequent pregnancy as previously reported[15, 16]. Women who had GDM in previous pregnancies might have carbohydrate intolerance to some degree that not only they were at higher risk for GDM but also that GDM could be diagnosed early in pregnancy. Previous reported associated risk factors for early diagnosis of GDM included older age, higher BMI, and family history of diabetes[9, 10]. Different findings might probably be due to different in risk criteria for early GDM screening in each setting.

GWG among early GDM women was significantly lower than those without GDM and they were also less likely to gain weight greater than recommendation. The findings were similar to the results from other studies[8, 13] This could probably be due to early nutritional and behavioral interventions provided to this group of women as the result of early diagnosis. Although rate of insulin requirement has been reported to increase among early GDM[7, 10, 12], the result of this study showed that while 13% of early GDM required insulin therapy, none of late GDM did, with borderline significance (p = 0.057) probably due to limited number of cases.

Many adverse outcomes associated with early diagnosis of GDM have been reported, including hypertensive disorders, perinatal mortality, neonatal hypoglycemia, asphyxia, NICU admission[6-10]. However, in this study, many GDM-related pregnancy outcomes were comparable between the 3 subgroups, but it should be noted that, although rates of both LGA and macrosomia were similar between early and late GDM, they seem to be higher than those without GDM. Significant increase in LGA and macrosomia among early GDM have been observed in some previous

studies[12, 13].

Some limitations of this study should be noted. Although all the women diagnosed with GDM received uniform counseling and management, the effects of both nutritional and pharmacological therapy could not be assessed. In addition, the degree to which those interventions affect pregnancy outcomes could not be evaluated. A specific screening and diagnostic strategies used in this study were also different from those of other studies that the results could not be compared directly. There might be some contaminations of women with unknown pre-pregnancy diabetes in the study samples due to the nature of a 2-step approach for GDM screening. However, the proportion of this group should be minimal and would not deviate the results significantly. Samples in subgroup analyses were also limited that there might be limited power to determine significant differences between groups.

The results of this study showed that majority of GDM could be diagnosed early in pregnancy, which supported the use of early universal GDM screening. However, further studies are needed to evaluate the use of screening protocol in other aspects, as well as its benefits in reducing adverse pregnancy outcomes.

Conclusion

In conclusion, prevalence of early GDM was 14.4% which contributed to 71.9% of all GDM cases. Pregnancy outcomes were not significantly different between early, late GDM and those without GDM. Both early and late GDM had slightly increase in rates of LGA and macrosomia. Previous GDM was the only independent factor associated with early GDM.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Randomised Trial on Intravenous Paracetamol versus Intramuscular Nalbuphine as Obstetrics Analgesia in First Stage of Labour

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ABSTRACT

Objectives: Labor pain is one of the most extreme pains ever described in the human experience, and different centers may have different standards and available pharmacologic options for managing labour pain. This study aimed to compare the efficacies of intravenous paracetamol and intramuscular nalbuphine for intrapartum analgesia.

Materials and Methods: We conducted a randomized controlled study from April 2019 to March 2020 in the Department of Obstetrics and Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan. This study involved 80 primigravidae who fulfilled the inclusion criteria and were randomly divided into two groups. The control group received 10 mg intramuscular nalbuphine, whereas the treatment group received 1,000 mg (100 mL vial) of intravenous paracetamol, infused over 15 minutes. Pain assessment before the administration of drugs and at 1 hour, 2 hours, and 3 hours post medication was recorded. Secondary outcomes, such as neonatal outcomes and maternal adverse events, were recorded.

Results: Demographic and clinical data between these two groups were similar. The mean pain score for the control and treatment groups before medication administration was 6.76 and 6.66, respectively. The mean pain score was 5.06 in the control group and 6.09 in the treatment group at 1-hour post medication, 6.19 and 6.89 at 2 hours post medication, and 7.51 and 7.57 at 3 hours post medication, respectively. No statistically significant difference in the mean pain score was found between the groups. However, more maternal adverse events were seen in the control group. No neonatal adverse events were reported in both groups.

Conclusion: Intravenous paracetamol showed no difference in intrapartum analgesic effect compared to intramuscular nalbuphine. However, in this study, we found out it has far fewer maternal adverse events.

Keywords: intravenous paracetamol, intramuscular nalbuphine, intrapartum analgesia, maternal adverse events, fetal adverse events.

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Introduction

Labour is the active process of delivering a fetus and is characterized by regular, painful uterine contractions that increase in frequency and intensity as parturition approaches. The intensity of labor pain faced by every woman has been found to affect the progress of labor, fetal outcome, and maternal physiological and psychological well-being.

Ideally, intrapartum analgesics should have high potency. However, the best choice of pain relief is determined by the available facilities and by a team of experts. Systemic opioids have been widely used for intrapartum analgesia; however, they are associated with maternal and fetal adverse events. These concerns have led to an exploration of alternative non-opioids for intrapartum analgesia.

Intravenous (IV) paracetamol is an effective antipyretic and non-opioid analgesic for treating moderate pain. Paracetamol has a central analgesic effect mediated through the activation of descending erotogenic pathways, inhibiting prostaglandin synthesis in the central nervous system and peripherally blocking pain impulse generation[1, 2]. Paracetamol has been used for a century, and its efficacy and tolerability are well established. However, there is a paucity of studies assessing its intrapartum use. Previous studies have shown that the analgesic effect of paracetamol is similar to that of a few types of opioids, and it has a favorable safety profile[3-6].

At our centre, we use intramuscular (IM) nalbuphine for intrapartum analgesia. Nalbuphine is a unique mixed agonist-antagonist in which a kappa-opioid receptor agonist as analgesia and a partial mu-opioid receptor antagonist which provides ceiling effect nausea, pruritus, and respiratory depression when compared to morphine[7]. It has been used as intrapartum analgesia and showed fewer side effects compare to other opioids[8-10]. Our extensive literature review revealed that no studies to date have compared IV paracetamol to IM nalbuphine. Hence, the current study aimed to compare the analgesic efficacy of IV paracetamol as intrapartum analgesia to that of IM nalbuphine and assess for maternal and neonatal adverse events.

Materials and Methods

This study was a randomized controlled trial performed from April 2019 to March 2020 in the Department of Obstetrics and Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan.

Approval to conduct this study was obtained from the Human Medical Research and Ethics Committee of Universiti Sains Malaysia (Ethics Approval Number: USM/JEPeM/18110756) and the Medical Research and Ethics Committee of the Ministry of Health, Malaysia (Ethics Approval Number: NMRR-18-3168-44683). This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki by the World Medical Association, the Malaysian Guideline for Good Clinical Practice, and other applicable regulatory requirements.

Written informed consent was obtained from primigravidae in labor who fulfilled the inclusion criteria. The inclusion criteria were singleton pregnancy at term in spontaneous labor without any risk factors (e.g. diabetes mellitus, hypertension, heart disease, blood-borne infectious diseases like hepatitis B/C or human immunodeficiency virus (HIV), liver disease or renal impairment) and a body mass index (BMI) of 18 - 30 kg/m^2. Women with a history of a scarred uterus, medical disorders, use of any analgesic before

recruitment, fetal distress or hypersensitivity to paracetamol or nalbuphine, and those who did not complete 4 hours in the study were excluded.

After enrolment, each participant was allocated the next available number in a concealed sequence of a computer-generated randomization plan that determined which drug was to be administered. The participants were randomly allocated into two groups. In the paracetamol (intervention) group, patients received an IV infusion of 1,000 mg paracetamol contained in a 100-mL vial over 15 minutes. In the nalbuphine (control) group, patients received 10 mg IM nalbuphine (1 ampoule, 1 mL = 10 mg). The recommended dose for IV paracetamol is 15 mg/kg, whereas that of nalbuphine is 10 - 20 mg 3 - 6 hourly with a maximum dose of 160 mg[11].

The drugs were immediately given after the artificial rupture of membranes (ARM) or the lack of membranes and when cardiotocography (CTG) was normal. The study drugs were prepared and administered by a staff nurse who was not involved in the assessment of outcome measures. Both medications were available in the labor room. Participants reported pain intensity by scoring on a visual analogue ccale (VAS; 0 = no pain; 10 = worst pain). Pain assessment was performed by a medical officer in the labor room who had no role in participant enrolment. Pain assessment before administering drugs and at 1 hour, 2 hours, and 3 hours post medication was recorded. Participants who had not delivered within 4 hours and still needed analgesics were given another dose of treatment (a minimum interval between each administration is 4 hours). A participant who requested rescue analgesics before the expected time (before 4 hours of labor) received Entonox® inhalation.

Labour was managed actively, using a partogram to monitor the maternal well-being (vital signs; blood pressure, pulse, temperature, pain score, urine output, hydration, and drug administered), fetal well-being (liquor, fetal heart rate, formation of caput or molding) and progress of labor (cervical dilatation, descend of fetal presentation, and uterine contraction). Duration of the first stage of labor, CTG, mode of delivery, and any intrapartum complication and maternal adverse events were recorded. Following delivery, birth weight, Apgar scores at 1 minute and 5 minutes, and any neonatal complications such as immediate neonatal respiratory problems and neonatal intensive care unit (NICU) admission were recorded.

Sample size calculation

The sample size of the study was calculated using the Power and Sample size (PS) software.

Significance level = 0.05, power = 80%, m = 1:1. The primary outcome VAS score measure was used to calculate the sample size. The parameters used in this sample size determination were the mean difference = 1.0, SD for paracetamol = 1.35[12] and p value of comparing analgesic effects of group paracetamol and placebo = 0.007. It was calculated that a minimum sample size of 30 women in each group would be needed to observe this difference at a similar or narrower confidence interval. Assuming a dropout rate of 20%, the sample size was set to 40 in each group. Thus, the total sample size is 80.

Data were analyzed using SPSS version 24 for Windows. A probability value of < 0.05 was considered to be statistically significant with a 95% confidence interval (CI). Descriptive data were expressed as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. The median and interquartile range were used to express skewed data. Demographic data, baseline characteristics, and primary and secondary outcome measures of both the groups were compared using an independent t-test and chi-squared/Fisher's exact test. Repeated-measures analysis of variance (ANOVA) was conducted to study the efficacy of IV paracetamol (intervention group) and IM nalbuphine (control group) based on pain scores using VAS. First, within-group analysis was performed to determine the individual effects within each group based on the VAS score. Second, between-group analysis was performed to compare the effects of each group treatment based on VAS score regardless of time. Lastly, within-between group analysis was used to compare the treatment effects between the two groups based on time. Multivariate analysis was performed for the VAS -

treatment interaction results based on the F-test. We used (two-way) repeated-measures ANOVA to test the hypothesis and determine the mean difference between groups (independent group and within group) at three repeated time points and also an interaction between each group and time.

The association between maternal adverse events and the study groups was tested using Pearson's chi-squared test. An independent t-test was used to compare fetal adverse events and Apgar scores at 1 minute and 5 minutes between the two groups. The association between fetal adverse events and CTG and the study groups was tested using Fisher's exact test.

Results

A total of 80 pregnant women were recruited and completed the study. Forty women were randomly included in the intervention group and 40 were designated as controls. The flow chart for patient recruitment is shown in Fig. 1.

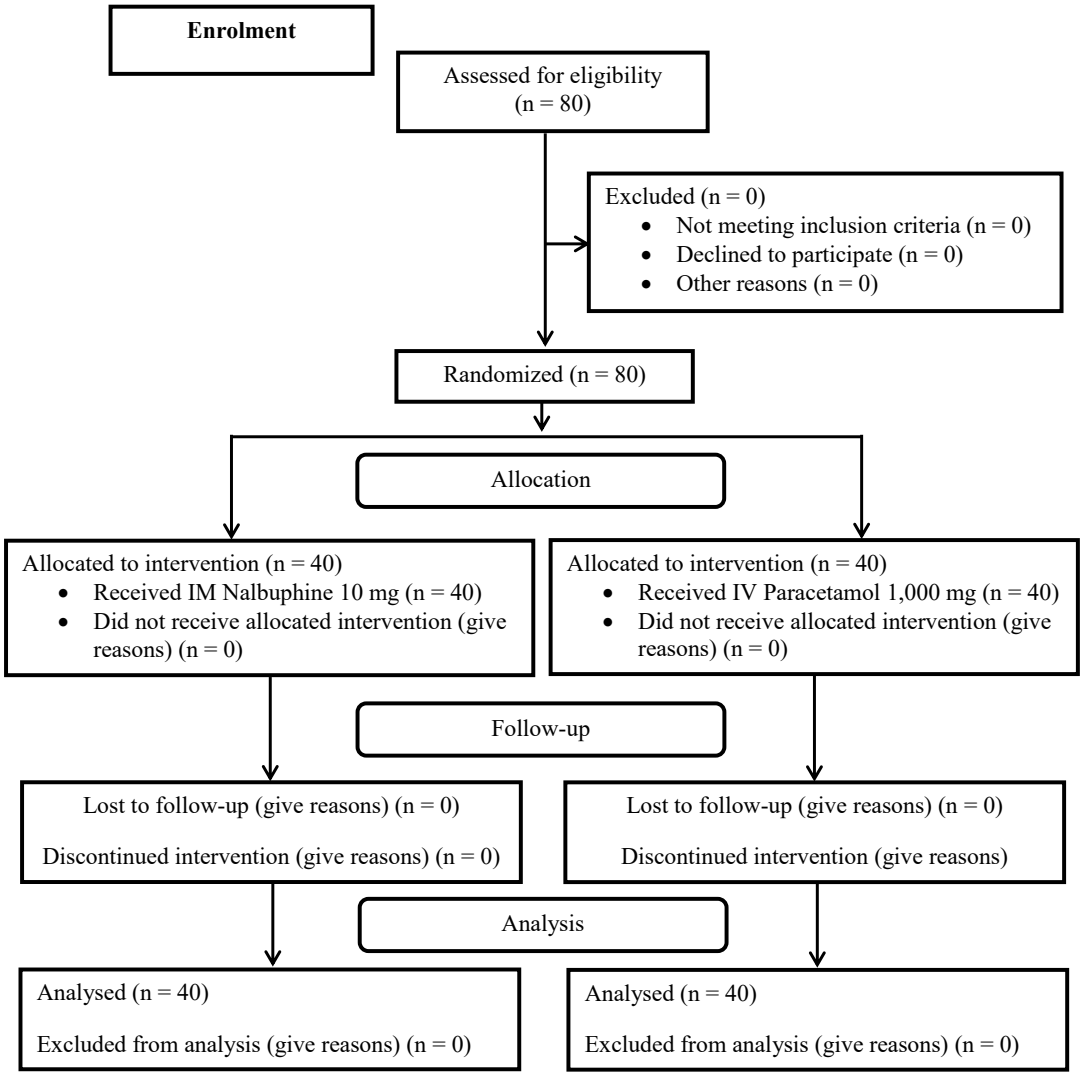

Fig. 1. Trial profile of this randomized controlled trial on IV paracetamol versus IM nalbuphine as intrapartum analgesia.

IM: intramuscular, IV: intravenous.

The mean age of the control group was 24.70 ± 3.65 years, and the mean age of the intervention group was 25.00 ± 2.84 years. All participants belonged to the Malay ethnic group. All participants were at term. Sixty-eight (85.0%) participants had ARM, whereas 12 (15.0%) had spontaneous rupture of membranes.

Meanwhile, 49 (61.3%) participants were on oxytocin so that all patients achieved four strong contractions in 10 minutes, of which, 45 (56.2%) presented with 4 cm cervical dilation, whereas 23 (28.8%) and 12 (15.0%) presented with 5 cm and 6 cm dilations, respectively. Only 2 (2.5%) patients required rescue analgesia in the control group and 3(3.75%) in the treatment group. A total of 60 (75.0%) participants delivered by spontaneous vaginal delivery, whereas 8 (10.0%) and 12 (15.0%) participants delivered by instrumental delivery and lower segment Cesarean section, respectively. The mean duration of labor for participants in the control and intervention groups was 4.47 (1.49) and 5.23 (2.34) hours, respectively. The maternal and labor characteristics are described in Table 1.

Table 1. Maternal and labor characteristics of enrolled patients.

Maternal characteristics	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	p value
Age	24.70 (3.65)†	25.00 (2.84)†	0.683*
Weight	55.00 (9.00)†	56.00 (10.00)†	0.849*
Height	154.85 (5.46)†	154.75 (4.98)†	0.932*
BMI	24.47 (3.89)†	24.39 (2.81)†	0.918*
Gestation on admission			0.304**
37 - 38^{+6}	19 (23.8)	14 (17.5)	
39 - 40^{+6}	18 (22.5)	19 (23.8)	
41 - 41^{+6}	3 (3.8)	7 (8.8)	
Oxytocin augmentation			0.251**
No	18 (22.5)	13 (16.3)	
Yes	22 (27.5)	27 (33.8)	
Rescue analgesia			0.644**
No	38 (47.5)	37 (46.3)	
Yes	2 (2.5)	3 (3.8)	
Dilatation of cervix			0.295**
4	22 (27.5)	23 (28.8)	
5	14 (17.5)	9 (11.3)	
6	4 (5.0)	8 (10.0)	
Mode of delivery			0.659**
Spontaneous vaginal delivery	30 (37.5)	30 (37.5)	
Caesarean section	7 (8.8)	5 (6.3)	
Instrumental delivery	3 (3.8)	5 (6.3)	
Duration of labour			0.091*
First stage (hours)	4.47 (1.49)†	5.23 (2.34)†	
Second stage (minute)	30.52 (16.40)†	28.78 (13.70)†	
Third stage (minute)	11.15 (6.51)†	10.74 (5.45)†	

† mean and standard deviation (SD). Otherwise, all values are in frequency and percentage. * Independent t-test. Otherwise, **Pearson Chi-square. BMI: body mass index

The distribution of outcomes in this study was described based on the primary and secondary outcomes. The primary outcome observed was the pain assessment after the administration of IV paracetamol (intervention group) and IM nalbuphine (control group). The primary outcomes are described in Table 2.

Table 2. Distribution of pain assessment based on the visual analogue scale scores and mean pain scores.

Pain	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	Mean difference (95% CI)	p value
Before injection	6.76 (1.91)	6.66 (1.86)	- 0.44 (- 1.34, 0.47)	0.339
After 1 hour of injection	5.06 (1.75)	6.09 (2.09)	- 0.69 (- 1.61, 0.21)	0.131
After 2 hours of injection	6.19 (1.84)	6.89 (2.03)	- 0.06 (- 0.89, 0.78)	0.891
After 3 hours of injection	7.51 (1.84)	7.57 (1.74)	- 1.19 (- 3.63, 1.25)	0.334

Repeated-measures ANOVA for within-between group analyses based on time was applied. Assumptions of normality, homogeneity of variances, and compound symmetry were checked and fulfilled. A p-value of < 0.005 indicated statistical significance.
CI: confidence interval

No significant difference was observed in the mean pain score between patients in the intervention and control groups based on VAS scores, regardless of the time in labor. As shown in Table 3, repeated-measures ANOVA was conducted to identify the within-group effects of each study drug based on time showing that there was a significant mean difference in each measurement time comparison within each group.

The secondary outcomes were maternal adverse effects during the medication period (Table 4).

Table 3. Comparison of within-group pain scores based on time (time effect).

Time	Control group (n = 40)		Intervention group (n = 40)	
	MD (95% CI)	p value	MD (95% CI)	p value
1 - 2 hours post injection	- 0.54 (- 0.94, - 0.14)	0.005	- 0.80 (- 1.26, - 0.34)	< 0.001
1 - 3 hours post injection	- 1.87 (- 2.52, - 1.21)	< 0.001	- 1.49 (- 2.13, - 0.85)	< 0.001
2 - 3 hours post injection	- 1.32 (- 1.93, - 0.72)	< 0.001	- 0.69 (- 1.08, - 0.29)	< 0.001

Repeated-measures ANOVA for within-group analyses was applied followed by multiple comparisons. Bonferroni correction was applied. A p value of < 0.05 indicated statistical significance. MD: mean difference, CI: confidence interval

Table 4. Distribution and association between maternal adverse effects and study group.

Maternal adverse effects	Control group (n = 40) n (%)	Intervention group (n = 40) n (%)	p value
Dizziness	8 (10.0)	1 (1.2)	0.001*
Nausea and vomiting	4 (5.0)	0 (0.0)	0.001*

* Fisher's exact test.

Twelve out of 40 patients in the control group experienced dizziness, nausea, and vomiting, whereas, in the intervention group, only 1 out of 40 patients complained of dizziness.

Fetal adverse events are shown in Table 5. The Apgar scores at 1 minute and 5 minutes between the control and intervention groups were found not significantly different (p = 0.233 and 0.323, respectively) with a 95% CI of mean difference (- 0.13, 0.53; - 0.10, 0.30, respectively).

Table 5. Distribution and association between fetal adverse effects and study group.

Foetal adverse effects	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	p value
Apgar scores at 1 minute	8.88 (0.56)	8.68 (0.89)	0.233
Apgar scores at 5 minutes	10.00 (0.00)	9.90 (0.63)	0.323
CTG			0.675[a]
Suspicious/abnormal	28 (35.0)*	39 (48.8)	
Normal	12 (15.0)*	1 (1.2)	
Birth weight (kg)	3.05 (0.41)	3.18 (0.38)	0.160[b]
Respiratory problem immediate post delivery	0 (0.0)*	0 (0.0)*	
Admission to NICU	0 (0.0)*	0 (0.0)*	

* Frequency and percentage. Otherwise, all values are in mean and standard deviation (SD). Fischer's exact test. b Independent t-test.
CTG: cardiotocography, NICU: neonatal intensive care unit

Discussion

We conducted a single-center randomized clinical study to compare IV paracetamol with IM nalbuphine for pain relief in labor on a group of primigravidae and found no significant difference in pain scores. Interestingly, adverse maternal events were significantly lower in the IV paracetamol-treated group. Every birth experience is different, and the degree of pain may vary between individual pregnancies. Labour pain is complex and subjective and can vary greatly. It is a multifactorial physiological phenomenon that varies in intensity among women and is subject to social and cultural modifiers. Multiple pharmacological options are available to help women manage labor pain. The optimal analgesic effect is still regional anesthesia; however, with limited skilled staff, limited equipment, and high economic cost, it cannot be made routinely accessible to all. While opioids are effective substitutes, they cause marked side effects in both mother and fetus, including maternal nausea, vomiting, and drowsiness[8-11, 13, 14]. Pethidine is the most commonly used opioid worldwide[13, 14].

The in-hospital labour analgesic at Raja Perempuan Zainab II is IM nalbuphine (10 mg). A previous study showed that the analgesic efficacy of nalbuphine is comparable to that of pethidine; however, the side effects may also be similar, i.e. nalbuphine also induces nausea and vomiting[8, 10, 13-15]. Concerns regarding the side effects on women and babies suppress the usage of opioid medication for labor analgesia.

In this study, the patient sociodemographic characteristics were comparable between the control and treatment groups (Table 1). All our patients were primigravidae and had no previous experience of labor pain. This is an important factor to prevent biased results. Other factors influencing labor pain and delivery include maternal psychological state, mental preparation, family support, cultural background, and size and presentation of the fetus[16]. However, these other factors were not specifically considered in this study. Of particular note, since all patients belonged to the same

on oxytocin augmentation, with comparable prevalence between the two groups. The comparison is shown in Table 2, in which the number of patients on oxytocin augmentation in the control and treatment groups was 22 and 27, respectively. This is important in view of the aggravated pain usually caused by oxytocin in labor.

The mean duration of labor in the control and intervention groups was 4.47 and 5.23 hours, respectively. This finding contradicted that of previous studies, which demonstrated a remarkably shorter mean drug-to-delivery interval with paracetamol than with either tramadol or pethidine[3, 5]. The overall duration of labor between the two groups in our study did not differ significantly. Furthermore, cervical dilation before analgesic administration was also comparable between the groups (Table 1). Thus, the clinical presentation and handling of participants in both groups were also similar.

We successfully demonstrated that IV paracetamol for intrapartum analgesia was as effective as IM nalbuphine. The analgesic effect of paracetamol peaks at 1 hour following administration. This was demonstrable with a reduction in the mean pain score at 1 hour compared with the pre-treatment pain score (Table 2). The mean VAS score at 1 hour in the nalbuphine group was 5.06 and 6.09 in the paracetamol group. Both groups showed similar patterns in the rise and fall of VAS scores. The high pre-treatment pain scores amongst the patients in our study were likely due to the patient recruitment coinciding with the active phase of labor during which analgesia is deemed most needed. However, at 3 hours, the mean score increased even higher than the pre-treatment score. The onset of action of paracetamol occurs within 5 - 10 minutes of administration for a total duration of approximately 4 - 6 hours[17]. The increased mean score at 3 hours of treatment may be contributed by labor progress, which would be accompanied by increasing contraction pain intensity and frequency.

This study found no significant difference in the mean pain scores between patients in the intervention and control groups. Furthermore, the comparison revealed no statistically significant difference in pain scores at 1, 2, and 3 hours post-injection between the two groups ($p = 0.312$, 0.223, and 0.891, respectively). This was similar to previous findings in which the onset of analgesia after IV paracetamol occurred within 5 minutes, peaking at 40 - 60 minutes and lasting 4 - 6 hours[18]. The increase in the mean VAS score at 2 - 3 hours may indicate diminished clinical effect or accelerated pain because of labor progress.

The numbers of patients who required rescue analgesia were similar in both the groups, two in the control group and three in the treatment group. We gave Entonox to patients who had intolerable pain despite receiving analgesic treatment. This is the finding that supports the usage of these drugs as intrapartum analgesia as less than 10% of patients in each group required rescue analgesia. The pain is subjective and the accelerated pain because of Pitocin usage and progress of labor make the use of pain scoring cannot be used as the only indicator of the drug effect intrapartum. Most comparative studies involved IV paracetamol pitted against opioids such as tramadol and pethidine[3-6]. Although these trials used different opioids, they consistently showed reduced pain scores in the paracetamol group, thus indicating similar pain relief effects.

Common side effects of nalbuphine include drowsiness, dizziness, headache, nausea and vomiting, whereas the most commonly reported side effects of IV paracetamol are nausea and vomiting. In this study, more adverse events were observed in the nalbuphine group, whereas in the paracetamol group, only one patient experienced dizziness, indicating a favorable side effect profile for paracetamol (Table 4). This finding was consistent with that of other studies[1-21].

Neonatal outcomes were favorable in both groups. Most of our patients delivered babies with good Apgar scores who did not require NICU admission. Four cases of suspicious fetal heart tracing were reported in the nalbuphine group and two cases in the paracetamol group. However, at the time of delivery, the babies obtained good Apgar scores (Table 5). These findings confirm the absence of any clinically significant adverse neonatal effects with the use of the either drug. None

of the neonates required narcain post-delivery. All pharmacologic relief for intrapartum analgesia has side effects, either for the mother or the fetus. The placental transfer of nalbuphine is high, rapid, and variable, with a mother-to-fetus ratio ranging from 1:0.37 to 1:6.00. Foetal and neonatal adverse events have been reported, including fetal bradycardia, respiratory depression at birth, apnoea, cyanosis and hypotonia[23]. One study reported fetal heart rate flattening in 54% of cases and one neonate with a low Apgar score[25]. Paracetamol is considered safe for use in pregnancy, although a small amount of active drug may cross the placenta[6]. Paracetamol also has a non-selective inhibitory action on peripheral and central cyclooxygenase (COXs) and they may also contribute to explaining more recent proposed positive effects of paracetamol such as the closure of a patent ductus arteriosus (PDA) in the preterm, and other unwanted effects of paracetamol such as issues related to atopy, fertility and/or neurobehavioral following perinatal exposure during the first and second trimester[22]. The short-term safety has been documented and it is safe to use as intrapartum analgesia in term gestation[12, 22].

The outcome of this study gave an additional option of intrapartum analgesia available at our hospital, and the cost implication should be considered in the usage of this analgesia.

Limitations

VAS scoring was a subjective tool in this study. It was also impossible to blind the subjects, trial coordinator, and assessor because the drugs were dispensed without any camouflage.

Future equivalent and non-inferior trials should be conducted to show that intravenous paracetamol is recommended as intrapartum analgesia as it may have an equivalent effect with fewer side effects.

Conclusion

Intravenous paracetamol showed no difference in intrapartum analgesic effect compared to intramuscular nalbuphine. However, in this study, we found out it has far fewer maternal adverse events.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Single Blade Forceps versus Manual Delivery of Fetal Head during Cesarean Section: A randomized controlled trial

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ABSTRACT

Objectives: We aimed to compare the efficacy of single blade forceps versus manual delivery during cesarean section vis-à-vis time to deliver the fetal head and maternal and neonatal outcomes.

Materials and Methods: One hundred and forty-four pregnant women were randomly assigned to single blade forceps or manual delivery. The women were term, singleton, cephalic presentation, undergoing a low transverse cesarean section under spinal anesthesia. The primary outcome was time to deliver the fetal head. The secondary outcomes included operative time, maternal outcomes (unintended excision of uterine incision, uterine vessels injury), neonatal outcomes (Apgar scores at 5 and 10 min, oxygen need for resuscitation, and neonatal injury), and surgeon satisfaction.

Results: Baseline characteristics were comparable between groups except for the type of skin incision. Median time to delivery of the fetal head using single blade forceps was statistically shorter than using the manual delivery (24.50 s (interquartile range (IQR), 10.50 - 41.50) vs. 45.00 s (IQR, 19.50 - 92.00), $p < 0.001$). Similar results occurred for operative time, maternal outcomes, neonatal outcomes, and surgeon satisfaction. Minor neonatal injury was 9.72% in the single blade forceps group.

Conclusion: Using single blade forceps shortened the delivery of the fetal head during cesarean section without serious maternal and neonatal complications. Minor neonatal injury was more common in the single blade forceps group than the manual delivery group.

Keywords: single blade forceps, manual delivery, time to delivery of fetal head, cesarean section.

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การใช้คีมข้างเดียวเทียบกับการใช้มือในการช่วยคลอดศีรษะทารกระหว่างการผ่าตัดคลอด: การทดลองแบบสุ่ม

รัตน์ศักดิ์ ตั้งเทอดชนะกิจ, อุษณีย์ สังคมกำแหง, ธนนิตย์ สังคมกำแหง

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิผลการช่วยคลอดศีรษะทารกในการผ่าตัดคลอดระหว่างการใช้คีมข้างเดียวหรือการใช้มือในเรื่องระยะเวลาการคลอด ภาวะแทรกซ้อนมารดาและทารก*

วัสดุและวิธีการ: *สตรีตั้งครรภ์เดี่ยวครบกำหนดที่มีส่วนนำของทารกเป็นศีรษะ ได้รับการผ่าตัดคลอดโดยระงับความรู้สึกด้วยการฉีดยาชาเข้าช่องไขสันหลัง จำนวน 144 คน ถูกสุ่มเป็นสองกลุ่มคือใช้คีมข้างเดียวช่วยคลอด เปรียบเทียบกับการใช้มือช่วยคลอด ผลลัพธ์หลักคือระยะเวลาที่ใช้ในการคลอดศีรษะทารก ผลลัพธ์รองคือระยะเวลาในการผ่าตัดคลอด ภาวะแทรกซ้อนมารดา (การฉีกขาดมดลูกเพิ่มเติมจากรอยผ่าตัด, การบาดเจ็บของหลอดเลือดที่มาเลี้ยงมดลูก) ผลต่อทารก (การประเมินสภาวะทารกแรกเกิดที่ 5 และ 10 นาที การใช้ออกซิเจนในทารก การบาดเจ็บขณะช่วยคลอดทารก) และความพึงพอใจของแพทย์ผู้ผ่าตัด*

ผลการศึกษา: *ลักษณะทางประชากรศาสตร์ไม่แตกต่างกันระหว่างกลุ่มยกเว้นชนิดของแผลผ่าตัดที่ผิวหนัง ค่ามัธยฐานของระยะเวลาในการช่วยคลอดศีรษะทารกในกลุ่มใช้คีมข้างเดียวน้อยกว่าในกลุ่มใช้มือช่วยคลอดอย่างมีนัยสำคัญทางสถิติ (กลุ่มคีมข้างเดียว 24.50 วินาที (interquartile range (IQR), 10.50-41.50), กลุ่มมือ 45.00 วินาที (IQR, 19.50-92.00), $p < 0.001$) และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระยะเวลาในการผ่าตัดคลอด ภาวะแทรกซ้อนมารดา ผลต่อทารกและความพึงพอใจของแพทย์ผู้ผ่าตัด การบาดเจ็บเล็กน้อยในทารกพบได้ร้อยละ 9.72 ในกลุ่มที่ใช้คีมข้างเดียวช่วยคลอด*

สรุป: *การใช้คีมข้างเดียว ลดระยะเวลาในการช่วยคลอดศีรษะทารกระหว่างการผ่าตัดคลอดได้อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับการใช้มือช่วยคลอด โดยไม่พบภาวะแทรกซ้อนที่อันตรายต่อมารดาและทารกโดยการบาดเจ็บเล็กน้อยต่อทารกพบในกลุ่มที่ใช้คีมข้างเดียวมากกว่าการใช้มือช่วยคลอด*

คำสำคัญ: *การใช้คีมข้างเดียว, การใช้มือช่วยคลอด, ระยะเวลาในการคลอดศีรษะทารก, การผ่าตัดคลอด*

Introduction

Cesarean section is a major obstetric surgical procedure used to deliver a viable fetus and placenta through an incision in the abdominal and uterine walls[1-2]. The procedure is often performed when vaginal delivery would be harmful to the mother or fetus. In the USA, the rate of cesarean section decreased from 31.9% in 2018 to 31.7% in 2019[3]. By comparison, the rate in Thailand rose from 15.2% in 1990 to 58% in 2019[4-6].

Typically, cesarean delivery of the fetal head in cephalic presentation is by manual extraction using the hand slipped into the uterine cavity between the pubic symphysis and the fetal head. The head is gently elevated with palm and fingers through the incision then modest pressure is applied to the transabdominal fundus to deliver the fetal head[7]. The most challenging aspect is fetal head extraction through the uterine incision, which can be problematic in about 10% of cases[8-9]. Prolonged uterine manipulation and fetal head compression during a difficult delivery can induce neonatal hypoxia due to minimization of uteroplacental blood flow[10-11]. Uterine fetal head delivery intervals of greater than 3 min are associated with fetal hypoxia, fetal acidosis, and a low Apgar score[11-14]. In addition, surgeons may encounter problems when using their hand to deliver the fetal head if the size of the hand results in unintended extension (tearing) of the uterine incision[15-16]. Several techniques can thus facilitate safe delivery for the mother and child of the fetal head in cesarean section (viz., forceps extraction or vacuum extraction)[17].

The effectiveness and safety of techniques to deliver the fetal head during cesarean section have been reported. Vacuum extraction of the fetal head may harm the fetus due to scalp abrasions, retinal hemorrhages, jaundice, and cephalhematomas[15]. By comparison, double-blade forceps delivery of the fetal head might harm the fetus due to scalp injury[9]. Wahab and Abolouz reported that single blade forceps delivery of the fetal head did not differ from double blade forceps or manual delivery; in terms of uterine extension, uterine vessel injury, or additional stitches needed for repair[18]. There is inconclusive evidence with respect to the comparative efficacy of single blade forceps versus manual delivery of the fetal head during cesarean section. The current study thus focused on single blade forceps for assisted fetal head delivery during cesarean section.

The purpose of the current study was to compare two methods of cesarean fetal head delivery: single blade forceps versus manual delivery. The primary outcome was time to deliver the fetal head. The secondary outcomes were operative time, adverse maternal outcomes (unintended extension of uterine incision, uterine vessels injury, additional stitches to repair injury, uterine incision hematoma), neonatal outcomes (birth weight, Apgar scores at 5 and 10 min, oxygen needed for resuscitation, and neonatal injury), and surgeon satisfaction.

Materials and Methods

The current randomized controlled study was performed at Khon Kaen Hospital (Thailand) and was approved by the Khon Kaen Hospital Institute Review Board for Human Research (KEF63009). The study included pregnant women 18 and over, term, singleton, cephalic presentation undergoing elective low transverse cesarean section under spinal anesthesia with intrathecal spinal morphine. Exclusion criteria were cesarean section with indications, including: non-reassuring fetal heart rate, fetal distress, maternal obstetric complications (pregnancy-associated hypertension, antepartum hemorrhage, placenta previa, placental abruption, ruptured vasa previa, and uterine rupture), major fetal structural anomalies[19], death fetus in utero, uterine anomalies, and deeply engaged fetal head. The latter refers to a condition in which cesarean delivery of the fetal head requires a disimpaction technique including abdomino-vaginal approach or push technique, and in such cases manual or single blade forceps cannot be used to assist in extraction of fetal head[9].

The presentation, position, and engagement of the fetus were verified and recorded before the operation. Women who met the eligibility criteria were

enrolled. Participants were then informed about the study and reassured regarding expertise and confidentiality. Computer software was used to generate a list with group allocation using sealed opaque envelopes. Block of four randomization was applied using a 1:1 ratio. All participants who joined the study signed informed consent at the labor room or obstetric wards, and were randomized into two groups at the operating room prior to surgery by a nurse.

The first group underwent assisted extraction of the fetal head using single forceps (Simpson-Braun 36 cm, 14 ¼"). The second group underwent manual-assisted extraction of the fetal head. In order to close the gap in delivery experience, all residents and staff who performed cesarean section were instructed how to use single blade forceps to deliver a fetal head.

All pregnant women underwent a standard, routine, preoperative evaluation, including laboratory testing (complete blood count (2 ml) at labor room or obstetrics ward) and antibiotic prophylaxis for cesarean section, as per the standing order approved by the Ethics Committee and staff of the Obstetric and Gynecologic Department, Khon Kaen Hospital.

The operation followed surgical safety protocols and was initiated with an appropriate Pfannenstiel or low midline skin incision with a scalpel. The subcutaneous incision and rectus sheath was opened and extended with scissors or electrocautery. The peritoneum was opened, and pelvic organs identified. The bladder was gently separated from the lower uterine segment with dissection of the vesicouterine flap. The lower uterine segment was opened by scalpel, and then an incision made to the fetal membrane in order to deliver the fetal head. The delivery of the fetal head was accomplished by single blade forceps or manually with proper transabdominal fundal pressure by surgeon assistance.

The on-duty nurse measured the time to delivery of the fetal head using a stopwatch (ZSD-Stopwatch ZSD-013 (Black)). The timing started after applying the single blade forceps (or when manual extraction began) until full delivery of the fetal head.

For the single blade forceps group, if the fetal head was left occiput anterior (LOA), left occiput transverse (LOT), left occiput posterior (LOP), the left handle of the forceps was placed between the fetal head and the surgeon's dominant hand, and the cephalic curve was placed along the left side of the fetal head. If the fetal head was right occiput anterior (ROA), right occiput transverse (ROT), or right occiput posterior (ROP), the right handle of the forceps was placed between the fetal head and the surgeon's dominant hand, and the cephalic curve was placed along the right side of the fetal head. Finally, if the fetal head was occiput anterior (OA) or occiput posterior (OP), the surgeon rotated the fetal head to LOA, LOT, LOP, ROA, ROT, or ROP and applied as above.

The other group was the manual-assisted extraction of the fetal head. First, the surgeon's dominant hand slipped into the lower segment of the uterine cavity between the pubic symphysis, and the fetal head was gently elevated with palm and fingers through the incision.

If the delivery of the fetal head took more than three minutes, the surgeon applied double blade forceps to assist delivery. The rest of the operation followed the method of a standard cesarean section. During the operation, the following were recorded: time to deliver the fetal head, operative time, maternal outcomes (unintended extension of uterine incision, uterine vessel injury, additional stitches to repair injury, uterine incision hematoma, and difference in maternal hemoglobin), neonatal outcomes (birth weight, Apgar scores at 5 and 10 min, oxygen need for resuscitation and neonatal injury), and surgeon satisfaction. After the cesarean section, all women received standard postoperative care. Blood work included: postoperative complete blood count (2 ml) 24-h[20] at the obstetrics ward.

The sample size was calculated by two independent means using the mean time to deliver the fetal head from a pilot study (n = 30). The time to deliver the fetal head in the single blade forceps group was 25.40 ± 19.84 s vs. 44.33 ± 50.19 s in the control group. We set the type I error at 0.05 with a power of 80%. The calculation of sample size was 64 per group. When combined with dropout rate of 10%, 144 participants (72 in each group) were recruited. This research was conducted on an intention-to-treat basis and statistics were calculated using Stata version 12. The student

t-test and Mann-Whitney U test were used to analyze the between-group continuous variables. The Chi-square and Fisher's exact test were used to analyze the categorical variables. Descriptive statistics included means, standard deviations (SDs), or medians, and interquartile ranges (IQRs). Differences were considered statistically significant when the p value was < 0.05.

Results

Two hundred and fifty-six women were counseled for participation in the study. Excluded from the study were 112 women due to (a) refusal to participate (n = 77); (b) maternal obstetric complications including pregnancy-associated hypertension (n = 21), placenta previa (n = 1), or placental abruption (n = 1); (c) non-reassuring fetal heart rate (n = 8); or (d) deeply engaged fetal head (n = 4).

One hundred forty-four women were randomized into the single-blade forceps and manual delivery groups. In the single blade forceps group, one woman did not undergo the intervention as a random assignment in accordance with fetal face presentation. Meanwhile, 72 women in the manual delivery group received an intervention by random allocation. Six women in the single blade forceps group and eight women in the manual delivery group received the double blade forceps intervention to deliver the fetal head. None of the patients in either group withdrew from the study. Each group included 72 women in the final analysis (Fig. 1).

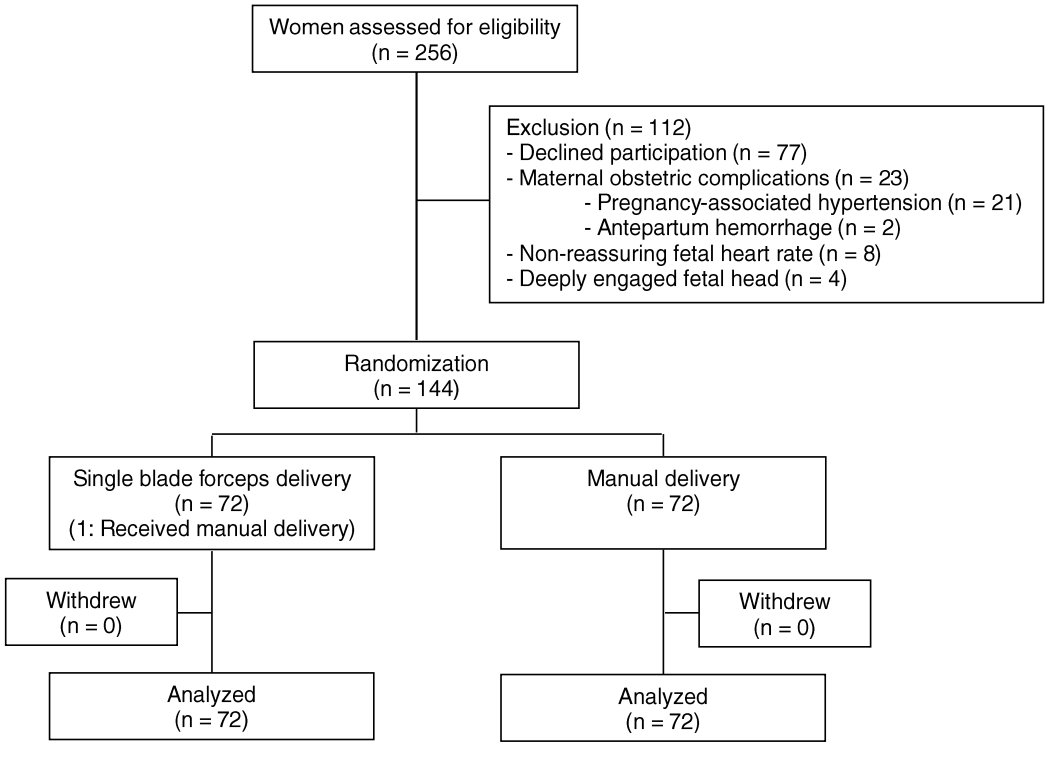

Fig. 1. Study flow.

Baseline characteristics were similar between groups, namely: maternal characteristics (age, gestational age, body mass index, parity, preoperative hemoglobin), surgical characteristics (indication of cesarean section, surgeon status), and neonatal characteristics (fetal head status) (Table 1). The exception was skin incision, where the proportion of Pfannenstiel incisions to low midline incisions was significantly greater in the single blade forceps group than the manual delivery group (p = 0.02).

Table 1. Baseline characteristics.

Characteristic	Single blade forceps delivery (n = 72)	Manual delivery (n = 72)	p value
Maternal characteristics			
Age (years), mean ± SD	29.85 ± 5.74	30.31 ± 5.34	0.62
Gestational age (weeks), mean ± SD	38.79 ± 0.80	38.78 ± 0.82	0.92
BMI (kg/m^2), mean ± SD	29.58 ± 4.17	29.72 ± 5.36	0.86
Parity, n (%)			0.37
Nulliparous	25 (34.72)	20 (27.78)	
Multiparous	47 (65.28)	52 (72.22)	
Pre-operative hemoglobin (g/dL), mean ± SD	12.03 ± 1.21	12.26 ± 1.13	0.24
Surgical characteristics			
Indication of cesarean section, n (%)			0.87
Previous cesarean section	36 (50.00)	39 (54.17)	
Cephalopelvic disproportion	28 (38.89)	25 (34.72)	
Others	8 (11.11)	8 (11.11)	
Skin incision, n (%)			0.02
Pfannenstiel	56 (77.78)	43 (59.72)	
Low midline	16 (22.22)	29 (40.28)	
Surgeon status, n (%)			0.85
Resident 1	5 (6.94)	4 (5.56)	
Resident 2	15 (20.83)	17 (23.61)	
Resident 3	11 (15.28)	14 (19.44)	
Staff	41 (56.95)	37 (51.39)	
Neonatal characteristics			
Fetal head status, n (%)			0.15
Head float	18 (25.00)	26 (36.11)	
Head engage	54 (75.00)	46 (63.89)	

BMI: body mass index, SD: standard deviation, n: number of patients

Time to delivery of the fetal head was the principal consequence and estimated at a median of 24.50 s (IQR, 10.50-41.50) in the single blade forceps category compared with 45.00 s (IQR, 19.50-92.00) in the manual category ($p < 0.001$). The secondary outcomes were not statistically different between the single blade forceps and manual delivery groups-namely, operative time (48.35 ± 17.62 min vs. 48.88 ± 18.89 min, p = 0.86); unintended extension of uterine incision (3 (4.17%) vs. 1 (1.39%), p = 0.31); uterine vessel injury (1 (1.39%) vs. 2 (2.78%), p = 0.56); additional stitch to repair injury (10 (13.89%) vs. (7 (9.72%), p = 0.44); hematoma at uterine incision (2 (2.78%) vs. 1 (1.39%), p = 0.56); proportion of surgeon satisfaction (69 (95.83%) vs. 66 (91.67%), p = 0.30); and, maternal hemoglobin change from preoperative to postoperative day 1 (median 0.80 g/dL (IQR, 0.07-1.30) vs. 0.90 g/dL (IQR, 0.40-1.70, p = 0.14). Neonatal outcomes had no remarkable differences between the single blade forceps and manual delivery groups-namely, birth weight; Apgar scores at 5 min or Apgar scores at 10 min; and, oxygen

therapy in newborns (equally both groups: 69 neonates did not use supplemental oxygen, 1 neonate used oxygen mask, tube, or oxygen box, 2 neonates used positive pressure ventilation). The 7 neonatal injuries included a mild degree of redness of the cheeks and chin and were found only in the single blade forceps group (9.72%) (Table 2). There were no serious neonatal injuries in either group.

Table 2. Primary and secondary outcomes.

Outcome	Single blade forceps (n = 72)	Manual delivery (n = 72)	p value
Primary outcome			
Time to delivery of fetal head (s), median (IQR)	24.50 (10.50 - 41.50)	45.00 (19.50 - 92.00)	< 0.001
Secondary outcomes			
Maternal outcomes			
Operative time (min), mean ± SD	48.35 ± 17.62	48.88 ± 18.89	0.86
Change in maternal hemoglobin between preoperative and postoperative day 1 (g/dL), median (IQR)	0.80 (0.07-1.30)	0.90 (0.40-1.70)	0.14
Adverse maternal outcomes			
Unintended extension of uterine incision, n (%)	3 (4.17)	1 (1.39)	0.31
Uterine vessel injury, n (%)	1 (1.39)	2 (2.78)	0.56
Additional stitch to repair injury, n (%)	10 (13.89)	7 (9.72)	0.44
Hematoma at uterine incision, n (%)	2 (2.78)	1 (1.39)	0.56
Neonatal outcomes			
Birth weight (grams), mean ± SD	3,230.69 ± 465.23	3,206.67 ± 407.87	0.74
Apgar scores at 5 min, n (%)			NA
Apgar scores < 7	0 (0)	1 (1.39)	
Apgar scores ≥ 7	72 (100.00)	71 (98.61)	
Apgar scores at 10 min, n (%)			NA
Apgar scores ≥ 7	72 (100.00)	72 (100.00)	
Minor neonatal injury, n %)	7 (9.72)	0 (0)	0.01
Surgeon satisfaction, n (%)	69 (95.83)	66 (91.67)	0.30

IQR: interquartile range, SD: standard deviation, n: number of patients

Discussion

Single blade forceps significantly shortened delivery of the fetal head during cesarean section (24.50 s (IQR, 10.50-41.50) vs. 45.00 s (IQR, 19.50-92.00), p < 0.001). Secondary outcomes were not significantly different between groups-namely, operative time, maternal outcomes (unintended extension of uterine incision, uterine vessels injury, additional stitch to repair injury, uterine incision hematoma), neonatal outcomes (birth weight, Apgar scores at 5 and 10 min, oxygen need for resuscitation), or surgeon satisfaction. The rate of minor neonatal injury was 9.72% in the single blade forceps group.

To our knowledge, no study has compared time to deliver the fetal head during cesarean section using single blade forceps versus manual delivery. Wahab and Abolouz did compare manual, single blade forceps and double blades forceps, and the primary outcome was discomfort or pain during fetal head delivery[18]. They did not, however, evaluate time to deliver of fetal

head in their study[18]. The respective median time in the single blade forceps category vs. the manual delivery category was 24.50 vs. 45.00 s: the difference being statistically but not clinically significant. The type of skin incision affected the time to deliver the fetal head because (a) the Pfannenstiel (transverse) skin incision provided less operating space (exposure) than the low midline (vertical) skin incision[21], and (b) the latter was predominately used in the single blade forceps group. Importantly, delivery of the fetal head was faster in the single blade forceps group than the manual delivery group. The fact that the single blade forceps reduced the time to delivery by about 20.5 s might have decreased adverse outcomes (i.e., blood loss from a uterine incision).

The primary outcome was consistent with Swain et al[22] who compared time to deliver the fetal head between the vacuum, double forceps, and manual methods. The double forceps-assisted delivery was shorter than the manual group as reported by Swain et al[22] in contrast to Bofill et al[23] who found that the manual group was faster than the double forceps group. The double forceps and vacuum-assisted delivery methods produced similar results according to Swain et al[22] To contrast, Bofill et al[23]observed that the vacuum-assisted method was faster than the double forceps delivery method. According to both research teams, the vacuum-assisted delivery method was faster than the manual method.

The secondary outcomes were operative time, adverse maternal outcomes (i.e., unintended extension of the uterine incision, uterine vessel injury, additional stitches to repair injury, and uterine incision hematoma), and neonatal outcomes (i.e., birth weight, Apgar scores at 5 and 10 min, oxygen need for resuscitation, and neonatal injury). The secondary outcomes were similar between groups, except for neonatal injury. The finding was consistent with Wahab et al who reported no significant differences for delivery of the fetal head between the single blade forceps and manual delivery methods vis-à-vis uterine extension, uterine vessel injury, or additional stitches to repair injury[18]. Similarly, Bofill et al reported no significant difference between the vacuum, forceps, and manual methods vis-à-vis uterine incision extension, post-operative hemoglobin, and hemoglobin drop[23]. Swain et al summarized that the manual method resulted in greater extension of the uterine incision than the forceps and vacuum methods, and that there was no significant difference in estimated blood loss between the manual and vacuum methods, even though the forceps method was hypothesized to have greater blood loss.

Mild neonatal injuries (e.g., red lesion) only occurred in the single blade forceps group (n = 7; 9.72%). There were no serious injuries in either group, as also reported by Swain et al[22] and Bofill et al[23]. Swain et al described 300 at-term cases of cesarean section presenting with a high floating fetal head. The study-assessing the three methods: forceps, vacuum, and manual extraction)- revealed that 2 of 100 cases in the forceps group had a minor scalp injury[22]. Meanwhile, Bofill et al reported that use of instruments (forceps or vacuum), at the time of an elective repeat cesarean section in 44 women, permitted a delivery that was as safe for the mother and infant and easy and effective for the mother and physician as traditional manual delivery[23]. There were also no serious neonatal injuries: the Apgar scores at 5 min was comparable to Swain et al with no significant difference between groups[22].

The strengths of the current study were that (a) it was a randomized controlled trial, thereby reducing confounding factors between groups; (b) none of the patients lost to follow-up; and (c) the sample size was adequate. The limitations were that (a) it was not possible to mask the surgeons and nurses to the allocation of the use of single blade forceps, and (b) we did not measure blood loss during the cesarean section.

Conclusion

Single blade forceps was an alternative method to manual delivery with a shortened time to deliver the fetal head during cesarean section with non-significant complications. Minor neonatal injury was more common in the single blade forceps group than the manual delivery group.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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