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EDITORIAL

This third issue of Thai Journal of Obstetrics and Gynaecology (TJOG) contains many interesting articles. The special article in this issue is "**Fertility-Sparing Treatment in Endometrial Cancer"**.

RTCOG Annual Meeting 2019 will be held during 15-18 October 2019 at Dusit Thani Pattaya Hotel, Chonburi, Thailand. The theme of this meeting is "**OBG62 Next Gen**". This meeting will have **AOFOG** session on the topic "**Current Controversies in O&G Practice**". All RTCOG members are cordially invited to participate this scientific meeting.

Residents who would like to publish their researches in TJOG should submit their works before September 30, 2019. Our editorial team and constructive reviewers will let them know the results before December 31, 2019.

Editor in Chief already attended "**Editors Day Thailand 2019**" on April 26th, 2019 at Prachasangkom Udopathana meeting room, Institute for Population and Social Research, Mahidol University Salaya, Phutthamonthon, Nakhon Pathom, Thailand and the Thai Journal Citation Index meeting: "**The 7th TCI-TRF-Scopus Collaboration Project**" on Friday 5th July 2019 at Sala Thai Room, 3rd Floor, Ambassador Hotel, Bangkok, Thailand.

This year, TJOG has prepared for the 4th round re-evaluation for TCI indexed journals (2020-2024). Thus, there are many changes of the journal during this time.

Wish to see you at RTCOG Annual Meeting 2019 at Dusit Thani Pattaya Hotel, Chonburi, Thailand

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

Thai Journal of Obstetrics and Gynaecology
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SPECIAL ARTICLE

Fertility-Sparing Treatment in Endometrial Cancer

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ABSTRACT

Endometrial cancer is one of the most common gynecologic cancers in Thailand. Approximately 15-25% of women are diagnosed during their premenopausal period. Standard treatment of endometrial cancer includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with staging procedures. However, conservative management with progestin therapy may be considered in selected patients for fertility preservation. Candidates for fertility-sparing treatment are women with early stage, well differentiated endometrioid adenocarcinoma without myometrial invasion. Oncologic and fertility outcomes of patients treated with conservative management are limited. Therefore, close surveillance is needed during conservative management. Definitive treatment should be performed after completion of childbearing.

Keywords: endometrial cancer, fertility-sparing treatment, progestin.

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Introduction

Endometrial cancer is one of the most common gynecologic cancers in Thailand with an incidence rate 2.9 per 100,000 women[1]. In developed countries, the incidence rate was reported to be higher at approximately 12.9 per 100,000 women[2,3]. Most patients with endometrial cancer are diagnosed during their postmenopausal period. Meanwhile, approximately 15-25% of patients are diagnosed before menopausal period and 3-5% of them are under age 40[3-5]. Common risk factors for developing endometrial cancer in young women are obesity, hypertension, nulliparity, early menarche and chronic anovulation with obesity being the most common risk factor[6]. Younger women with endometrial cancer are more likely to be diagnosed at early stage, having well differentiated, endometrioid type adenocarcinoma and having favorable prognosis than their older counterparts[7-9].

Standard treatment for endometrial cancer includes total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) with peritoneal washing and pelvic/paraaortic lymph node dissection. Young women with early stage endometrial cancer carry an excellent prognosis. Additionally, reproductive-age

women frequently have delayed childbearing, resulting in an increasing in number of nulliparous women at the time of endometrial cancer diagnosis. In order to preserve fertility in young patients, selected patients should be provided the conservative management options.

Candidates for fertility-sparing treatment

The National Comprehensive Cancer Network (NCCN) guidelines recommend fertility-sparing option for management of endometrial cancer in patients with early stage, well differentiated (grade 1) endometrioid adenocarcinoma with disease limited to the endometrium and no evidence of suspicious or metastatic disease[10].

Tissues for histologic diagnosis can be obtained by dilatation and curettage (D&C), endometrial biopsy and hysteroscopic biopsy. However, preferred method for histologic diagnosis is D&C[10]. Histologic grade of tumor from endometrial biopsy and D&C was reported to be upgraded in 26% and 10% of cases after hysterectomy, respectively[11]. Regarding hysteroscopic evaluation and biopsy, risk of peritoneal spread of endometrial cancer during the procedure is concerned[12,13]. Importantly histologic subtype and grade of tumor should be documented and reviewed by expert gynecologic pathologist.

Contrast-enhanced magnetic resonance imaging (MRI) is the preferred method to determine myometrial invasion. Its sensitivity and specificity in detecting myometrial invasion were approximately 75-80% and 94-96%, respectively[14]. Previous studies reported that MRI is more sensitive than ultrasonography for the evaluation of myometrial invasion (86-89% vs. 66-79%, respectively)[15,16]. Additionally, metastatic lesions and disease extension can be assessed by this imaging technique.

Hormonal treatment

Medical treatment with either oral progestins or levonorgestrel-releasing intrauterine device (IUD) can be considered for fertility-sparing treatment of endometrial cancer. Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most commonly used oral progestins[17-19]. However, their optimal dose, duration of treatment and route of administration are currently not well-defined. The most frequently used regimens are MA at a dose of 160 mg daily and MPA at a dose of 500-600 mg daily[20,21]. Previous studies reported greater regression and relapse rates with levonorgestrel-releasing IUD than oral progestins[22,23]. There are no randomized controlled trials to compare the effectiveness of these treatment modalities.

Surveillance and monitoring of progestin therapy

Close surveillance to evaluate the response of treatment is crucial in conservative treatment of endometrial cancer. Unfortunately, optimal surveillance protocol remains debatable. The NCCN guideline recommend close monitoring with tissue diagnosis obtained by either endometrial biopsy or D&C every 3-6 months[10]. Definitive treatment with total abdominal hysterectomy and BSO with staging procedure is recommended if patients demonstrate disease progression on the biopsy or endometrial carcinoma is present after 6-12 months of progestin therapy[10, 20, 24]. In patients with persistent endometrial carcinoma after 6 months of progestin therapy, pelvic MRI should be performed to exclude myometrial invasion and metastasis before continuing fertility-sparing therapy[10].

High rate of disease recurrence after completed regression was reported[10, 17-19].

Therefore, women who have complete regression should be encouraged to have prompt conception and definitive treatment is recommended after completion of childbearing.

Oncologic outcomes after progestin therapy

Previous studies reported the response rates between 42-62%[18, 19, 25, 26]. Varying in the response rates was likely a result of variation in treatment duration and difference in the definition of completed response. In addition, median times to completed response were also varied among studies. The most reported median time to response was approximately 4-6 months[17, 26-28].

The recurrence rates after fertility-sparing therapy were reported between 19.2-33.8%[17-19, 26, 29].

Reproductive outcomes

Most of the previous studies were small case series and aimed to determine oncologic outcome rather than pregnancy outcome. Therefore the pregnancy outcomes after fertility-sparing therapy are largely unknown. A recent meta-analysis which included 28 studies with 1,038 women with early stage endometrial carcinoma or complex atypical endometrial hyperplasia treated with progestin therapy reported the pooled pregnancy outcomes with pregnancy rate of 34%, and only 20% of them delivered live newborns[30].

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OBSTETRICS

Birth Weight/ Placental Weight Ratios: Does the association differ between early- and late-onset preeclampsia?

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ABSTRACT

Objectives: Early- and late-onset preeclampsia (PE) may differ in pathophysiology and this can be reflcted in differences in birth weight/placental weight (BW/Pl) ratios. Therefore, we compared BW/Pl ratios of births with early- and those with late-onset PE.

Materials and Methods: The retrospective descriptive study included all hospital-based singleton births of 24-43 weeks' gestation between January 2007 and December 2016. A total of 51,940 pregnant women were divided into three groups: early-onset PE, late-onset PE, and pregnant women without PE. Birth weight/placental weight were compared among 3 groups.

Results: The mean (± standard deviation; SD) BW/Pl ratios were signifiantly different in early-onset PE and late-onset PE compared with the control group (3.91 ± 0.93 in early-onset PE, 4.85 ± 0.91 in late-onset PE and 5.17 ± 0.90 in the control group, $p < 0.001$). The factors signifiantly associated with BW/Pl ratios were race, infant gender, diabetes mellitus (DM), gestational age at delivery, early-onset PE, late-onset PE, small for gestational age (SGA) and large for gestational age (LGA). After adjustment for DM, gestational age at delivery, late-onset PE, SGA and LGA, the BW/Pl ratio was still associated signifiantly more with early-onset PE than with late-onset PE.

Conclusion: The BW/Pl ratios of preeclamptic women differed between early- and late-onset PE, and that early-onset PE may be commonly associated with placental efficiency. This suggests that preeclampsia consists of several different processes manifesting as a single disease.

Keywords: preeclampsia, placenta, birth weight, early onset, late onset.

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อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก มีความแตกต่างกันหรือไม่ระหว่างหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว และเกิดขึ้นช้า

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บทคัดย่อ

วัตถุประสงค์: *ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วกับเกิดขึ้นช้า น่าจะมีพยาธิสรีรวิทยาการเกิดที่แตกต่างกันซึ่งจะส่งผลให้เกิดความแตกต่างระหว่างอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก การศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาความแตกต่างระหว่างอัตราส่วนดังกล่าวในครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า*

วัสดุและวิธีการ: *เป็นการศึกษาทบทวนข้อมูลภายในโรงพยาบาล ในหญิงตั้งครรภ์เดี่ยวที่คลอดตั้งแต่อายุครรภ์ 24-43 สัปดาห์ ระหว่างเดือน มกราคม พ.ศ.2550 ถึงเดือนธันวาคม พ.ศ. 2559 คิดเป็นจำนวนหญิงตั้งครรภ์ 51,940 ราย แบ่งออกเป็น 3 กลุ่มศึกษา ได้แก่ หญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว หญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้า และหญิงตั้งครรภ์ที่ไม่มีภาวะครรภ์เป็นพิษ ทำการเปรียบเทียบอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก*

ผลการศึกษา: *ค่าเฉลี่ย (± ค่าเบี่ยงเบนมาตรฐาน) ของอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกมีความแตกต่างกันอย่างมีนัยสำคัญระหว่างหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและชนิดเกิดขึ้นช้า เมื่อเทียบกับกลุ่มที่ไม่มีภาวะครรภ์เป็นพิษ (3.91±0.93 ในกลุ่มหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว, 4.85±0.91 ในกลุ่มหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้าและ 5.17±0.90 ในกลุ่มที่ไม่มีภาวะครรภ์เป็นพิษ, p<0.001) ตัวแปรที่มีผลต่ออัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกได้แก่ โรคเบาหวาน อายุครรภ์ ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า ทารกขนาดเล็กและใหญ่กว่าอายุครรภ์ ภายหลังควบคุมตัวแปร ได้แก่ โรคเบาหวาน อายุครรภ์ ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้าและทารกขนาดเล็กและใหญ่กว่าอายุครรภ์ อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกยังคงสัมพันธ์กับภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วมากกว่าภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้า*

สรุป: *อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกในหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า มีความแตกต่างกันอย่างมีนัยสำคัญ และพบว่ามีผลมากกว่าในกลุ่มที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว อาจเนื่องมาจากภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วมีผลจากรกเสื่อมมากกว่า และภาวะครรภ์เป็นพิษน่าจะเกิดได้จากหลายกระบวนการ*

คำสำคัญ: *ครรภ์เป็นพิษ, รก, น้ำหนักทารกแรกเกิด, เกิดขึ้นเร็ว, เกิดขึ้นช้า*

Introduction

Birth weight/placental weight ratios (BW/Pl ratio), calculated as the grams of fetal birth weight per gram of placenta weight, reflect placental efficiency or placental function[1,2]. The ability of the placenta to maintain nutrient delivery to the fetus has an influence on fetal birth weight, and it is well established that there is a positive correlation between placental weight and birth weight[3-5]. The BW/Pl ratio is often reduced, which may indicate a placenta that fails to adapt its nutrient transfer capacity to compensate for its small size[6].

Recent data have supported classifying preeclampsia (PE) into early-onset PE, which tends to develop before 34 weeks of gestation, and late-onset preeclampsia, which develops at or after 34 weeks of gestation[7,8]. Early- and late-onset PE have been found to be associated with different pathophysiological-specific features. Early-onset PE is commonly associated with placental dysfunction, reduction in placental volume, perinatal death and adverse maternal and neonatal outcomes[9,10]. Conversely, late-onset PE is more often associated with normal placenta, normal fetal growth and more favorable outcomes[11,12].

In this study, we hypothesized that early- and late-onset PE had different pathophysiology. Thus, we sought to compare BW/Pl ratios of early- and late-onset preeclampsia in order to explore the existence of these differences.

Materials and Methods

The present study was conducted at Rajavithi Hospital, a tertiary care teaching public hospital affiliated to Rangsit University in Bangkok, Thailand, with the ethical approval of the local institutional review board. The study included all hospital-based singleton births of 24-43 weeks' gestation between January 2007 and December 2016 (n=54,618). Deliveries after congenital anomalies (n=227), stillbirth (n=372), multiple gestations (n=994) and deliveries with missing gestational age, placental weight or birth weight (n=953) were excluded.

Descriptive analyses were performed on all study variables. Implausible values and potential errors were excluded, including birth weights above or below the mean by three standard deviations (SD), placental weights that were <100 g or >1,000 g and unknown or ambiguous genders (n= 132). The final sample was 51,940 singleton deliveries.

Preeclampsia (PE) was defined as a resting blood pressure ≥ 140/90 mmHg and proteinuria of > 300 mg/L or a 2^+ urine dipstick after 20 weeks of gestation in a previously normotensive woman[13]. Small for gestational age (SGA) was defined as infants with birth weight below the 10^{th} centile for gestational age, and large for gestational age (LGA) was defined as infants with birth weight above the 90th centile for gestational age based on the King Chulalongkorn Memorial Hospital's nomogram of birth weight for gestational age at delivery[14].

Untrimmed placenta weight (including the membranes and umbilical cord) and birth weight of the infant were weighed in grams immediately after delivery. The birth weight/placental weight ratio (BW/Pl ratio) was then calculated.

The cases were divided into three groups: early-onset PE (PE occurring at less than 34 weeks of gestation); late-onset PE (PE occurring at 34 or more weeks of gestation); and a control group (pregnancies without PE).

The data were presented as mean ± SD. Chi-square test was used to compare categorical proportion (nulliparous, race, infant gender, pre-gestational diabetes mellitus and gestational diabetes mellitus, SGA, and LGA). Multiple comparisons of maternal age, gestational age at delivery, placental weight, birth weight, and BW/Pl ratio in between groups were performed by one-way analysis of variance (ANOVA) followed by post hoc test adjustment with Bonferroni correction. Pearson's correlation, simple and multiple linear regression were analyzed for BW/Pl ratio. Data analysis was performed using the SPSS ver.16.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 with a 95% confidence interval (CI) was considered statistically significant.

Results

From January 2007 through December 2016, a

total of 51,940 pregnant women who had singleton hospital deliveries at 24 weeks of gestation or later and met the inclusion criteria were enrolled in the study. Those diagnosed with PE accounted for 2.7% of participants, of which 339 (0.65%) had early-onset PE, and 1,111 (2.14%) had late-onset PE. The demographic data are outlined in Table 1. The mean maternal age, race, pre-gestational and gestational diabetes mellitus (DM) and gestational age at delivery were significantly different in early-onset PE and late-onset PE compared with the control group, while the proportion of infant gender was significantly different between early-onset PE and the control group. Gestational DM was significantly different in the late-onset PE compared to the control group.

Table 1. Comparison of baseline characteristics data in different groups.

Variables	Early onset-PE (n = 339)	Late onset-PE (n = 1111)	Control (n = 50,490)	p value
Maternal age (yr), mean ± SD	29.64 ± 6.60[a)]	29.9 ± 7.04[a)]	27.5 ± 6.19	< 0.001[A]
Nulliparous (%)	197 (58.1%)	592 (53.3%)	26205 (51.9%)	0.05[C]
Thai race (%)	295 (87%)[a)]	923 (83.1%)[a)]	38632 (76.5%)	< 0.001[C]
Infant male gender (%)	150 (44.2%)[a)]	543(48.9%)	26133 (51.8%)	0.004[C]
Pre-gestational DM (%)	10 (2.9%)	29 (2.6%)[a)]	132 (3%)	< 0.001[C]
Gestational DM (%)	19 (5.6%)	134 (12.1%)[a)]	2421 (4.8%)	< 0.001[C]
Gestational age at delivery (weeks), mean ± SD	30.56 ± 2.21[a)]	37.15 ± 1.88	37.15 ± 1.85	< 0.001[A]

DM, diabetes mellitus

[a)] Statistical significance ($p < 0.05$)

[A] p value was tested by ANOVA followed by post hoc test adjustment with Bonferroni correction.

[C] p value was tested by chi-square.

A comparison of mean birth weight, mean placental weight, mean BW/PI ratio, SGA, and LGA is presented in Table 2. The mean (± SD) birth weights were 1,412 ± 479 grams in early-onset PE, 2,733 ± 612 grams in late-onset PE, and 3,036 ± 452 grams in the control group ($p < 0.001$). Mean (± SD) placental weights were 372 ± 127 grams in early-onset PE, 578 ± 145 in late-onset PE, and 601 ± 123 in the control group ($p < 0.001$). Mean (± SD) BW/PI ratios were 3.91 ± 0.93 grams in early-onset PE, 4.85 ± 0.91 grams in late-onset PE, and 5.17 ± 0.90 grams in the control group ($p < 0.001$), and these values were significantly different in early-onset PE and late-onset PE compared with the control group. SGA was significantly higher in early-onset PE (41.3%) and late-onset PE (10.6%) than in the control group (1.3%) ($p < 0.001$). LGA was significantly lower in early-onset PE (9.7%) than in the control group (15.7%) ($p = 0.009$).

Table 3 lists details of factors such as maternal age, race, infant gender, DM, gestational age at delivery, early-onset PE, late-onset PE, SGA and LGA that might be expected to have an influence on the BW/PI ratio. Univariate analysis indicated the factors influencing the BW/PI ratios, and showed that race, infant gender, DM, gestational age at delivery, late onset-PE, early onset-PE, LGA, and SGA were significantly associated with the BW/PI ratios. After multiple linear regression analysis, the significant factors associated with BW/PI ratio were DM, gestational age at delivery, late onset-PE, early onset-PE, LGA, and SGA (Table 4).

In all pregnant women in our study, birth

weight and placenta weight were correlated (r = 0.62, p < 0.001).

Table 2. Comparison of BW, PI, SGA, LGA and BW/PI in different groups.

Variables	Early onset-PE (n = 339)	Late onset-PE (n = 1111)	Control (n = 50,490)	p value
Mean BW ± SD (g)	1,412.4 ± 479.0[a)]	2,733.0 ± 611.7[a)]	3,036.0 ± 452.0	< 0.001[A]
Mean PI ± SD (g)	372.1 ± 127.3[a)]	577.6 ± 145.1[a)]	601.2 ± 122.7	< 0.001[A]
Mean BW/PI ± SD	3.9 ± 0.9[a)]	4.9 ± 0.9[a)]	5.2 ± 0.9	< 0.001[A]
SGA (%)	140 (41.3)[a)]	118 (10.6)[a)]	662 (1.3)	< 0.001[C]
LGA (%)	33 (9.7)[a)]	181 (16.3)	7,952 (15.7)	0.009[C]

BW, birth weight; PI, placenta weight; SGA, small for gestational age; LGA, large for gestational age.
[a)] Statistical significance (p < 0.05), [A] p value was tested by ANOVA followed by post hoc test adjustment with Bonferroni correction, [C] p value was tested by chi-square.

Table 3. Univariate analyses (95% confidence interval; CI) for BW/PI ratio.

Factors	BW/PI ratio				
	Mean	SD	B	95% CI Of B	p value
Maternal age (yr)	5.16	0.90	0.00	- 0.01, 0.01	0.871
Race					
Thai	5.13	0.91	Ref		
Others	5.25	0.87	0.12	0.10, 0.14	< 0.001
Infant gender					
Male	5.20	0.91	Ref		
Female	5.11	0.90	- 0.08	- 0.09, - 0.07	< 0.001
DM					
None	5.16	0.91	Ref		
DM	5.04	0.86	- 0.13	- 0.16, - 0.10	< 0.001
Gestational age at delivery (weeks)	5.16	0.90	0.10	0.10, 0.11	< 0.001
Preeclampsia					
None	5.17	0.90	Ref		
Late onset-PE	4.85	0.91	- 0.33	- 0.39, - 0.26	< 0.001
Early onset-PE	3.91	0.93	- 1.26	- 1.38, - 1.15	< 0.001
Fetal growth					
AGA	5.17	0.89	Ref		
LGA	5.13	0.93	- 0.04	- 0.06, - 0.01	0.002
SGA	4.72	1.18	- 0.45	- 0.52, - 0.38	< 0.001

B, beta coefficients; CI, confident interval; DM, diabetic mellitus; PE, preeclampsia; AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age

Table 4. Independent factors associated with BW/PI ratios by multiple linear regression.

Factors	BW/PI ratio				
	Mean	SD	B	95% CI Of B	p value
DM					
None	5.16	0.91	Ref		
DM	5.04	0.86	- 0.11	- 0.14, - 0.07	< 0.001
Gestational age at delivery (weeks)	5.16	0.90	0.10	0.09, 0.10	< 0.001
Preeclampsia					
None	5.17	0.90	Ref		
Late onset-PE	4.85	0.91	- 0.20	- 0.26, - 0.15	< 0.001
Early onset-PE	3.91	0.93	- 0.43	- 0.54, - 0.33	< 0.001
Fetal growth					
AGA	5.17	0.89	Ref		
LGA	5.13	0.93	0.07	0.05, 0.09	< 0.001
SGA	4.72	1.18	- 0.20	- 0.26, - 0.14	< 0.001

B, beta coefficients; CI, confident interval; DM, diabetic mellitus; PE, preeclampsia; AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age

Discussion

In this retrospective study conducted in Thailand between 2007 and 2016, the mean BW/PI ratio was significantly lower in pregnancies with early-onset PE than in those with late-onset PE and those in the control group (3.91 ± 0.93 vs 4.85 ± 0.91 vs 5.17 ± 0.90, respectively). Similarly, Kim et al[15] reported that the mean BW/PI ratio was significantly lower in the PE group than in the control group (5.1 vs 6.0 respectively). In a previous study[16-20], variables that may affect BW/PI ration were found to include infant gender, race, DM, gestational age at delivery, SGA, and LGA. Our study found that the factors significantly associated with BW/PI were DM, gestational age at delivery, early-onset PE, late-onset PE, SGA, and LGA. After adjustment for DM, gestational age, late-onset PE, SGA, and LGA, the BW/PI ratio was still associated with early-onset PE significantly more than with late-onset PE.

The placenta is important in providing a healthy environment for the fetus and plays a central role in the pathophysiology of PE. The placenta regulates its nutrient transfer efficiency by morphological and functional adaptations which result in optimal fetal growth[2, 21, 22]. In our study, mean birth weight and mean placental weight were significantly lower in the PE group, and when birth weight was divided by placental weight, it was still lower in the PE group. It has been postulated that PE is strongly associated with small placenta and that it has an influence on placental function results in a fetus that is small with respect to its genetic potential.

PE has collectively been termed ischemic placental disease because the two types are frequently characterized by utero-placental underperfusion, chronic hypoxia and placental ischemia, which are results of abnormal spiral artery remodeling, failed trophoblast invasion and impaired transformation of decidual spiral arteries leading to abnormal placentation and influencing placental efficiency[23-27]. It has been hypothesized that placental ischemia may reduce nutrient supply so that the fetal growth may be affected. A reduction in the BW/PI ratio may be indicative of

placental dysfunction. In keeping with the results of several previous reports[15, 28,29], the BW/PI ratio in this report was found to be reduced in births with PE. Another important finding in the current study was that the BW/PI ratio was still significantly lower in early-onset PE than in late-onset PE (mean difference = -0.2 vs -0.43 respectively). This finding supports the view that PE in early-onset PE is more commonly associated with placental dysfunction than with late-onset PE. The current data suggests that distinct vascular adaptation in early and late PE could reflect different pathophysiologic mechanisms[9, 10, 30, 31]. Further studies to correlate early- and late-onset PE with the pregnancy outcomes are warranted.

The strength of this study was that it had adjusted data which made the outcomes more reliable, and that it was one of a large series with a big enough sample size to have the power to distinguish the outcomes. To the best of our knowledge, no previous hospital-based study on BW/PI ratio of early- and late-onset PE has been published.

Some limitations of this study should be noted. First, the retrospective nature of this study based on computer searches might be associated with some incomplete data and can not select only uncomplicated, healthy pregnant woman in the control group. Secondly, the weight of placentas was considered as the sum of the weight of placenta, membranes and umbilical cord (untrimmed placenta).

Conclusion

In conclusion, the BW/PI ratio of preeclamptic women differed in cases of early- and late-onset PE, and that early-onset PE may be commonly reduce placental efficiency. This suggests that PE is composed of several different processes manifesting as a single disease.

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Potential conflicts of interest

The authors declare no conflict of interest.

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Correlation between Serum Dehydroepiandrosterone and Cognitive Function in Thai Pre/ Perimenopause Women Aged 40-49 Years Old: A cross-sectional study

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ABSTRACT

Objectives: To determine correlation between serum dehydroepiandrosterone (DHEA) and cognitive impairment as evaluated by the Montreal Cognitive Assessment (MoCA) in premenopausal/ perimenopausal women. The study also evaluated other factors those can affect both cognitive function and DHEA concentrations.

Materials and Methods: A cross-sectional, single population study recruited 101 healthy premenopausal/perimenopausal women aged 40-49 years. The inclusion criteria included participants who did not have i) hormonal treatment including DHEA, ii) previous ovarian operation, and iii) endocrinological, neurological and mental illness. Blood sampling and MoCA test were performed following the written informed consent. The MoCA, a cognitive screening test evaluating 8 compartments of global cognitive function, was all performed by single certified-physician. MoCA < 25 is determined as having cognitive impairment. DHEA concentrations were measured in batch utilizing the deMeditec ELISA kits.

Results: Mean age of the participants was 43.49 ± 2.89 years. Mean DHEA concentration was 16.07 ± 5.45 ng/ml while the MoCA score was 24.12 ± 3.44. Women with impaired cognitive function (MoCA < 25) were 44.6% (45/101). Neither correlation between DHEA-MoCA, Age-DHEA, nor Age-MoCA was observed (r = -0.139, -0.01, -0.12, respectively; $p > 0.05$). Only women's years of education was positively correlated with the MoCA score ($r = 0.469$, $p < 0.001$). Adjusted odd ratio of serum DHEA on low MoCA (< 25) score was 0.98 (95%CI 0.92, 1.06, $p = 0.649$ determined by log-regression analysis).

Conclusion: No correlation between serum DHEA concentration and cognitive function as determined by the MoCA score in the premenopausal/perimenopausal population aged between 40-49 years old.

Keywords: Dehydroepiandrosterone (DHEA), cognitive function, Montreal Cognitive Assessment (MoCA), Thai women.

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การวิจัยแบบตัดขวางเรื่องความสัมพันธ์ของระดับของฮอร์โมน DHEA และภาวะพุทธิปัญญาในหญิงไทย วัยก่อน/ใกล้หมดระดู อายุระหว่าง 40-49 ปี

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บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาความสัมพันธ์ระหว่างฮอร์โมน dehydroepiandrosterone (DHEA) และภาวะพุทธิปัญญาบกพร่อง โดยใช้แบบทดสอบ Montreal Cognitive Assessment (MoCA) ในผู้หญิงวัยก่อน/ใกล้หมดระดู ศึกษาปัจจัยอื่นๆ ทีมีผลต่อภาวะพุทธิปัญญา และระดับฮอร์โมน DHEA ในกลุ่มประชากรที่ศึกษา*

วัสดุและวิธีการ*: การศึกษาแบบตัดขวาง เก็บข้อมูลจากหญิงไทยอายุ 40-49 ปี จำนวน 101 ราย เกณฑ์คัดอาสาสมัครเข้า ประกอบด้วย 1. ไม่มีประวัติใช้ยาฮอร์โมน รวมถึง DHEA 2. ไม่มีประวัติผ่าตัดรังไข่ และ 3. ไม่มีโรคทางต่อมไร้ท่อ โรคทางระบบประสาทและโรคจิตเวช โดยทำการเก็บเลือดจากผู้เข้าร่วมวิจัยเพื่อตรวจระดับฮอร์โมน DHEA โดยวิธี ELISA และทำแบบทดสอบ MoCA เพื่อประเมินภาวะพุทธิปัญญา แบบทดสอบจะมีทั้งหมด 8 ส่วน ซึ่งทำการประเมินโดย ผู้ผ่านการฝึกอบรม โดยผลการประเมิน MoCA ต่ำกว่า 25 จะแปลผลได้ว่ามีภาวะพุทธิปัญญาบกพร่อง*

ผลการศึกษา*: ค่าเฉลี่ยอายุผู้เข้าร่วมการศึกษา 43.49±2.89 ปี ค่าเฉลี่ยของระดับฮอร์โมน DHEA 16.07±5.45 ng/ml และค่าเฉลี่ยของ MoCA score 24.12±3.44 คะแนน โดยมีผู้ที่ได้ MoCA score น้อยกว่า 25 คะแนน ซึ่งถือว่ามีภาวะพุทธิปัญญาบกพร่องอยู่ร้อยละ 44.6 จากผลการศึกษาไม่พบความสัมพันธ์ระหว่างฮอร์โมน DHEA กับ MoCA score อายุกับฮอร์โมน DHEA และอายุกับ MoCA score (r = -0.139, -0.01, -0.12 ตามลำดับ; $p > 0.05$) มีเพียงจำนวนปีการศึกษาที่มีความสัมพันธ์กับ MoCA score ($r = 0.469$, $p < 0.001$) Adjusted odd ratio ของฮอร์โมน DHEA กับระดับ MoCA score น้อยกว่า 25 คะแนน คือ 0.98 (95%CI 0.92, 1.06, $p = 0.649$ วิเคราะห์ข้อมูลโดยใช้สถิติ log-regression analysis)*

สรุป*: ไม่พบความสัมพันธ์ระหว่างฮอร์โมน DHEA และภาวะพุทธิปัญญาที่ประเมินโดยใช้แบบทดสอบ MoCA ในประชากรหญิงวัยก่อน/ใกล้หมดระดูอายุ 40-49 ปี*

คำสำคัญ*: Dehydroepiandrosterone, พุทธิปัญญา, แบบประเมินพุทธิปัญญา Montreal Cognitive Assessment*

Introduction

Ageing results in multiple organ deterioration, including cardiovascular, musculoskeletal, cognition, sexual function, etc. There has been a search for decades to explore solutions to fight against the ageing. It is established that a majority of hormonal axes, especially adrenal and gonadal steroids, are diminished with age. Hence, a concept of hormone fountain of youth was created in which hormone supplements and vitamins have been used to rejuvenate an individual's body[1]. One of the most common hormone medications used is dehydroepiandrosterone (DHEA) which can be prescribed over-the-counter in the Unites States as a food supplement to improve general well-being and prevention of ageing in elderly population (both men and women)[1]. DHEA is a steroid hormone mainly produced from the zona reticularis of the adrenal cortex[2]. DHEA level peaks at around age of 20 and decreases by approximately 10% in every 10 years[3]. Despite being under-investigated, previous studies have shown that it is linked to the conversion of sex hormones, i.e. estradiol (E2) and testosterone (T) in the peripheral organs, such as liver[4]. Due to its function as a substrate for potent sex steroid (both E2 and T) conversion, researcher has been determining to establish a link between diminishing DHEA with reproductive ageing. In fact, many subfertility women who are suffered from ovarian ageing either by their age or premature ovarian insufficiency have currently been prescribed DHEA as an adjuvant in their invitro fertilization cycles. Therefore, DHEA is not only used in an elder but also a young individual who is in needs (and is indicated) for 'anti-ageing' medication.

One of conditions mostly seeks for anti-ageing intervention is impaired cognitive function or dementia/Alzheimer's disease. Cognitive function is an intellectual process which includes contemplation, comprehension, reasoning and recollection of a domain of information, and it is affected by number of various factors, but the most recognizable one is aging. There are multiple tools accepted for the assessment of the cognitive function, including the Montreal Cognitive Assessment (MoCA), which can be used to detect early impairment in cognition. The MoCA relatively demonstrates higher sensitivity with a comparable specificity when compared to other tests such as the Mini-Mental State Examination (MMSE). MoCA assesses various domains of cognition such as visuoconstructional skills, naming, memory, attention, verbal fluency, abstraction and delay recall. The total score is 30, in which a score of greater than or equal to 25 is considered normal[5]. Previous studies demonstrated a correlation between DHEA and cognitive function in postmenopausal women, aged of more than 50, and showed a conflicting study results. The neuroprotective mechanisms of DHEA can be described by that i) studies has shown that E2 and T play a beneficial role in the cognitive function[6-9]. ii) neural tissue can synthesize DHEA. In addition, the DHEA is partially produced by the brain, and functioning as a neuroprotective hormone[10]. Nonetheless, current studies on menopausal women group with age of more than 50 have shown that the administration of DHEA is not associated with the improvement of cognitive function[11].

Currently, there is no study investigating the relationship between serum DHEA and cognitive function in the premenopausal population. As previously mentioned, conflicting findings were noted in the postmenopause and elderly population, those some studies observed an association between serum DHEA and cognitive function[12, 13] but supplying DHEA medication did not improve the cognitive function[11]. The inconclusive result thus makes it worth evaluating the association in the pre-/peri-menopausal women. DHEA constantly declines throughout women's life, thus may support or deny the positive correlation that some papers had suggested. Besides aging, hypoestrogenic state also negatively affects the cognitive function[6-9]. Thus, in this study, we focused on the pre/perimenopausal women who have decreased DHEA level, while the estrogen level still maintained. Moreover, we should

be able to gain information as a reference for future research whether serum DHEA can predict early cognitive impairment and may suggest patients for the supplementation. The objective of this study was therefore to evaluate a correlation between DHEA and cognitive function determined by the MoCA, specifically focusing on pre-/peri-menopause women aged between 40-49 years old. Correlations between age and either serum DHEA or the MoCA were also investigated. Finally, factors influencing the impaired cognitive function were determined using the multivariate model.

Materials and Methods

This cross sectional study recruited pre/perimenopausal women aged between 40 to 49 years, who visited the general gynecology department at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) during 2016 to 2017. This study received financial support from Faculty of Medicine, Srinakharinwirot University and was approved by the institutional ethical committee. The inclusion criteria consisted of female aged as described above who had i) their last menstrual period within one year before enrolled into the study, ii) no current hormone or steroid use, iii) no history of DHEA hormone supplement, iv) no history of ovarian surgery, v) no history of endocrinological disorder; such as polycystic ovarian syndrome (PCOS) or adrenal gland disorder, vi) no history of severe head injury or neurological diseases such as Alzheimer's disease, and vii) no history of mental disorders. Upon written informed consent obtained, participants were asked to provide their demographic information. Then cognitive function assessment was performed using the Thai version MoCA. Participant who could not complete the MoCA due to any reason, for example, illiteracy, would be excluded from the study.

MoCA is used to detect early impairment in cognition. On the other hand, scoring less than previously stated, is considered as impaired cognitive function[5]. The Thai version MoCA test have the sensitivity to detect mild cognitive impairment (MCI) of 80% and to detect a mild Alzheimer's disease (AD) of 98%, with the specificity of 80%[14]. In this study, the MoCA was done by the principal investigator (P.E.) who had been trained and certified through the MoCA official website, http://www.mocatest.org. Participants with an abnormal MoCA score should then be appointed for the neurological examination by the consultant neurologist (M.W.). Finally, 3-5 ml blood sample was collected by a qualified nurse for later DHEA analysis. Serum was separated from the blood sample by centrifugation at 4,000 rpm for 10 minutes and stored at -20°C until assay. Enzyme-linked immunosorbent assay (ELISA) of serum DHEA was carried out in batch once recruitment completed utilizing the DeMeditec ELISA kit (Germany). The intra- and inter-assay correlation coefficients were 7% and 10%, respectively.

Statistical analysis

The calculation of the sample size was done using a formula of single population, cross-sectional survey[15]. Because there had no data of a prevalence of impaired cognitive function in pre/peri-menopausal women from previous studies, neither Asian nor Western population, thus the prevalence of mild impaired cognitive function reported in the post-menopausal population was alternately entered in the formula[16]. The target population required 88 participants. A Total of 101 participants were recruited in this study. The descriptive data were shown as mean ± SD. The correlation between DHEA and MoCA score and other factors, were analyzed using linear regression analysis. Meanwhile, the correlation between DHEA and impaired cognitive function considering when MoCA score less than 25 was analyzed using the log regression analysis. Finally, for other factors and variables, including DHEA levels, that can influence the impairment of cognitive function, was analyzed using multivariate regression analysis.

Results

Table 1 demonstrates patient demographic

data. Mean ± SD age and body mass index (BMI) of the participants were 43.49 ± 2.89 years and 23.39± 3.50 kg/m^2, respectively. Approximately half of the participants was in the normal BMI range (18.5-22.9 kg/m^2). Mean years of education was 12.32 ± 4.64 years in which 57.4% of the cohort received > 12 years of education. Correspondingly, the most educational level was Bachelor degree or higher (56.4%). In the study population, mean ± SD serum DHEA concentration was 16.07 ± 5.45 ng/ml. A level of 5.17 and 26.97 ng/ml were considered as a lower and upper limit for normal DHEA concentration in this study. Mean ± SD MoCA score was 24.12 ± 3.44. MoCA score screening positive for impaired cognitive function (MoCA < 25) was observed in 44.6% of the total number of participants. Mean DHEA concentrations between the low (< 25) and normal (≥ 25) MoCA score were similar (16.35 ± 5.38 vs. 15.85 ± 5.54, p = 0.649). Adjusted odd ratio, determined by logistic regression analysis, of the serum DHEA concentrations in the low MoCA score over the normal group was 0.98 (95%CI 0.92, 1.06, p = 0.649) (Table 2).

Various correlations were determined. Regarding the MoCA score, neither serum DHEA concentration nor participant's age was observed to be correlated with the cognitive function (Pearson correlation coefficient, r=0.139, 0.120; p=0.167, 0.233, respectively). As expected, women's years of education was positively correlated with the MoCA score, r=0.469, p<0.001) (Table 3). Concerning serum DHEA levels, there is no significant correlation between either age or BMI and the DHEA concentrations (r=0.01, 0.144; p=0.920, 0.151, respectively). Adjusted correlation coefficients in the multivariate model is present in Table 3 and 4.

Table 1. Demographic data.

	n (%)	**Mean ± SD**
Age (years)		43.49 ± 2.89
• 40 - 44	68 (67.3)	
• 45 - 49	33 (32.7)	
BMI (kg/m^2)		23.39 ± 3.50
• < 18.5	4 (4)	
• 18.5 - 22.9	51 (50.4)	
• 23 - 24.9	23 (22.8)	
• 25 - 29.9	17 (16.8)	
	6 (6)	
Years of education (years)		12.32 ± 4.64
• ≤ 6	25 (24.8)	
• 7 - 12	18 (17.8)	
• > 12	58 (57.4)	
Highest educational level		
• Primary school	25 (24.8)	
• Secondary or vocational school	19 (18.8)	
• Bachelor or higher	57 (56.4)	

BMI: body mass index

Table 2. Subgroup analysis regarding DHEA concentrations, age and years of education between participants with normal cognitive function (MoCA score ≥ 25) and cognitive impairment (MoCA score < 25).

	Normal cognitive function MoCA ≥ 25	Cognitive impairment: MoCA < 25	p value
Total n (%)	56 (55.4)	45 (44.6)	
DHEA concentration (mean ± SD; ng/ml)	15.85 ± 5.54	16.35 ± 5.38	0.65
Age (mean ± SD; years)	43.49 ± 2.51	44.07 ± 3.23	0.08
Years of education (mean ± SD; years)	13.18 ± 4.53	10.89 ± 4.83	< 0.01

DHEA: dehydroepiandrosterone, MoCA: Montreal Cognitive Assessment

* Overall MoCA score in the population was 24.12 ± 3.44

** Adjusted odd ratio of serum DHEA on low MoCA (< 25) score was 0.98, 951%CI 0.92-1.06, p = 0.649

Table 3. Demonstrate correlation coefficients between MoCA score and other factors.

	Adjusted correlation coefficient (r)*	p value
DHEA	- 0.139	0.167
Age	- 0.120	0.233
Year of education	0.469	< 0.001

DHEA: dehydroepiandrosterone

Table 4. Demonstrate correlation coefficients between DHEA level and other factors.

	Adjusted correlation coefficient (r)*	p value
Age	0.01	0.920
BMI	0.144	0.151

BMI: body mass index

Discussion

Overall, there was no correlation between serum DHEA and cognitive function determined by the MoCA score. Likewise, a correlation between age and either MoCA or serum DHEA could not be detected in the study. Serum DHEA concentrations were similar between participants with normal and low (< 25) MoCA score. It is important to note that almost half of participants had their MoCA scores less than 25 which were compatible with mild cognitive impairment.

A majority of previous cross-sectional studies determining a correlation between serum DHEA and impaired cognitive function were conducted in either post-menopause or elderly population[10]. Valenti et al (2009) conducted a study in the elderly population, aged > 65 years old using Mini-Mental state examination (MMSE), one of the cognition tests, and they found that DHEA levels were positively related with the higher MMSE score[12]. Davis et al (2008), also studying in the postmenopausal women, found that DHEA concentrations were positively correlated

with the executive function, concentration and working memory[13]. Both studies enrolled a large number, approximately 300 of participants. In contrast, few studies, again in elderly population, failed to demonstrate a significant correlation[17, 18]. Moreover, various studies evaluated the efficacy of DHEA supplementation in post-menopausal women but the results were inconclusive[10]. For example, Merritt et al (2012) could not demonstrate a beneficial effect of 40 mg/day of oral DHEA for 4 weeks on an improvement of short term memory in women aged > 55 years old[19]. These conflicting results lead to our investigation in the younger population. We concluded that serum DHEA could not predict the cognitive impairment as determined by the MoCA test. The findings have also raised concerns over a beneficial effect of DHEA supplementation especially in a young individual. There was a possibility concerning a non-correlation result that our age group was too specific in which the variety of cognitive function among the study population. It can also imply that cognitive deterioration is a long-term, chronic process.

DHEA is secreted mainly to the circulation from the adrenal glands[2]. The original function of DHEA is thought to serve as a substrate for more potent sex-steroid conversion[4]. Estrogen stimulates neuron growth and formation of synapses, neurotransmitter production and functions as an anti-oxidant[20], thus provides a protective effect on the cognitive function[6-9]. In addition, DHEA can be produced and it works locally in the brain. Peripheral conversions as well as local production are believed to be a key explanation of our study, regarding the non-correlation result. In fact, Labrie and colleague reported similar findings in cognitive and other conditions which they then create the 'intracrine theory' supporting that serum DHEA level has a poor predictive factor as the hormone is actively converted at the target organ. The action of DHEA is therefore associated with rate and efficacy of hormone conversion (to either E2 or T) at the peripheral tissue[21].

Nonetheless, 44.6% of participants in our study had cognitive impairment as determined by the MoCA score. The number was also in accordance with the educational background of the study population in which 43.6% were graduated from lower than the Bachelor degree. Moreover, the study's subgroup analysis demonstrated a significant lower years of education in the participants with impaired cognitive function (MoCA < 25) when compared with the normal group (10.89 ± 4.83 vs 13.18 ± 4.53, $p < 0.01$) (Table 2). An increasing year of education was moderately correlated with higher MoCA score ($r = 0.469$, $p < 0.001$) (Table 3). In literature, it is also evidenced that higher education is significantly associated with better cognitive function[22]. Distribution of participant's education background was therefore a primary determining factor of the higher incidence of cognitive impairment among the study's participants. The unexpectedly high incidence was different from other previous studies especially the one utilized for sample size calculation (prevalence = 5%) and hence may required a bigger sample size to demonstrate a significant correlation. In addition, although the MoCA test demonstrated a better sensitivity, while the specificities were comparable, when compared to other tests such as the MMSE[23], the results were from studies performed in the elderly population Therefore, the accuracy of the test should be further explored in pre/perimenopausal population. In our groups, all participants with abnormal results were referred to the neurologist (MW, the 2nd author). There was no further intervention required for all test-abnormal participants.

Concerning the secondary outcomes, neither association between age and serum DHEA nor between age and cognitive function was observed. On the contrary, previous studies demonstrated a negative correlation between age and serum DHEA levels[3] as well as the cognitive function. The previous studies were performed across multiple age groups. As mentioned earlier, an explanation could be from narrow-range age group in our study. Other explanation included either the intracrine theory, or interference of educational background, or all of reasons

mentioned. Further research is required to dissect the mechanism/function of DHEA prior to encourage the use of DHEA supplementation to prevent impaired cognitive function in women.

Conclusion

In conclusion, there was no correlation between serum DHEA concentration and cognitive function as determined by the MoCA score in the premenopausal population aged between 40-49 years old.

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Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Efficacy of Intravenous Sedation, Paracervical Block and Paracervical Block with Lidocaine Spray on Pain Relief during Uterine Curettage in First Trimester Incomplete Abortion: Randomized clinical trial

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ABSTRACT

Objectives: To evaluate efficacy of intravenous sedation, paracervical block (PCB) and PCB plus lidocaine spray for pain relief during uterine curettage in first trimester incomplete abortion.

Materials and Methods: Randomized trial included 121 participants with incomplete abortion at gestational age less than 14 weeks who underwent uterine curettage. They were randomly assigned into three groups: intravenous sedation (meperidine 50 mg and diazepam 10 mg), PCB (5 ml of 1% lidocaine injected at the 4 and 8 o'clock positions of cervix) and PCB plus 10% lidocaine spray 20 mg at the cervix. Pain score was measured using a numerical rating scale (0-10) before, during uterine curettage being undertaken, immediately and 30 minutes after the procedure. Adverse effects were observed and participants' satisfactions were evaluated.

Results: Pain score during the uterine curettage was significantly different across the three treatment groups (median score of 5 in intravenous sedation group, 5 in PCB group, 4 in PCB plus spray group, $p = 0.001$). Further pairwise comparisons found significantly greater benefits on pain relief during the uterine curettage in PCB plus spray than both PCB and intravenous sedation groups ($p = 0.001$ and 0.002, respectively). Significant differences in pain scores across the three treatment groups were also observed immediately ($p = 0.025$), and 30 minutes after the procedure ($p = 0.003$). Satisfaction of pain relief was lower in the intravenous sedation than the PCB and PCB plus spray groups. The intravenous sedation group reported more nausea and dizziness, while the PCB group reported more symptoms of numbness than the other two groups.

Conclusion: Paracervical block plus 10% lidocaine spray had high efficacy in pain relief in incomplete abortion uterine curettage with fewer minor adverse effects of nausea and dizziness.

Keywords: incomplete abortion, uterine curettage, intravenous analgesia, paracervical block, lidocaine spray.

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ประสิทธิภาพในการลดความเจ็บปวดระหว่างการขูดมดลูกในสตรีที่แท้งไม่ครบในไตรมาสแรก : การศึกษาแบบสุ่มเปรียบเทียบระหว่างการให้ยาลดปวดทางหลอดเลือดดำ การฉีดยาชาเฉพาะที่บริเวณปากมดลูกและการพ่นยาชาชนิดละอองฝอยร่วมกับการฉีดยาชาเฉพาะที่บริเวณปากมดลูก

ภคพงศ์ เกิดทวี, ปิยวดี วุฒิกรสัมมากิจ, ปริญญา ชำนาญ

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินประสิทธิภาพของการให้ยาลดปวดทางหลอดเลือดดำ การฉีดยาชาเฉพาะที่บริเวณปากมดลูกและการพ่นยาชาชนิดละอองฝอยร่วมกับการฉีดยาชาเฉพาะที่บริเวณปากมดลูกในการลดความเจ็บปวดระหว่างการขูดมดลูกในสตรีที่แท้งไม่ครบในไตรมาสแรก*

วัสดุและวิธีการ*: ทำการศึกษาแบบสุ่มในอาสาสมัคร 121 รายที่แท้งไม่ครบอายุครรภ์น้อยกว่า 14 สัปดาห์ซึ่งเข้ารับการรักษาโดยการขูดมดลูก โดยสุ่มแบ่งเป็นสามกลุ่ม ได้แก่กลุ่มที่ได้ยาลดปวดทางหลอดเลือดดำ (เมเพอริดีน 50 มิลลิกรัม และ ไดอะซีแปม 10 มิลลิกรัม), กลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูก (1% ลิโดเคน 5 มิลลิลิตร ที่ข้างปากมดลูกตำแหน่ง 4 และ 8 นาฬิกา) และกลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกร่วมกับการพ่นยาชาชนิดละอองฝอย (10% ลิโดเคนสเปรย์ 20 มิลลิกรัม) ประเมินระดับความเจ็บปวดโดยใช้ numerical rating scale (0-10) ก่อนทำหัตถการ ระหว่างทำหัตถการ หลังทำหัตการทันที และหลังทำหัตถการ 30 นาที รวมถึงสังเกตผลข้างเคียง และสอบถามความพึงพอใจของอาสาสมัคร*

ผลการวิจัย*: ระดับความเจ็บปวดระหว่างการขูดมดลูกมีความแตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่มการศึกษาทั้งสาม (ค่ามัธยฐานเท่ากับ 5 ในกลุ่มที่ได้ยาลดปวดทางหลอดเลือดดำ, 5 ในกลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกและ 4 ในกลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกร่วมกับการใช้ยาชาชนิดละอองฝอย p = 0.001) การศึกษาเปรียบเทียบทีละคู่ พบว่าประสิทธิภาพในการลดปวดระหว่างขูดมดลูกในกลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกร่วมกับการใช้ยาชาชนิดละอองฝอยดีกว่ากลุ่มได้ฉีดยาชาเฉพาะที่บริเวณข้างปากมดลูกและกลุ่มที่ได้ยาลดปวดทางหลอดเลือดดำอย่างมีนัยสำคัญ(p = 0.001 และ 0.002 ตามลำดับ) และพบว่ามีความแตกต่างกันอย่างมีนัยสำคัญของระดับความเจ็บปวดระหว่างสามกลุ่มหลังหัตการทันที(p = 0.025)และหลังหัตถการ30 นาที(p = 0.003) ระดับความพึงพอใจต่อยาที่ได้รับในกลุ่มที่ได้ยาลดปวดทางหลอดเลือดดำน้อยกว่ากลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกและกลุ่มที่ได้ฉีดยาชาเฉพาะที่บริเวณปากมดลูกร่วมกับการใช้ยาชาชนิดละอองฝอย อีกทั้งกลุ่มที่ได้ยาลดปวดทางหลอดเลือดดำมีคลื่นไส้และมึนงงมากกว่า ในขณะที่กลุ่มที่ได้ฉีดยาชาเฉพาะที่*

บริเวณปากมดลูกพบว่ามีการซามากกว่าอีกสองกลุ่ม

***สรุป**: การฉีดยาซาเฉพาะที่บริเวณปากมดลูกร่วมกับใช้ยาซาลิโดเคนชนิดละอองฝอยมีประสิทธิภาพสูงในการลดความเจ็บปวดในหัตถการขูดมดลูกในสตรีแท้งไม่ครบโดยมีผลข้างเคียงคลื่นไส้และมึนงงน้อยกว่า*

***คำสำคัญ**: แท้งไม่ครบ, การขูดมดลูก, การให้ยาลดปวดทางหลอดเลือดดำ, การฉีดยาซาเฉพาะที่บริเวณปากมดลูก, การฟ่นยาซาชนิดละอองฝอย*

Introduction

Incomplete abortion is one of the most common obstetric problems. Bureau of reproductive health, Thailand reported data of 1,415 spontaneous abortion in 2015 with high rate of complications such as requirement for blood transfusion due to excessive hemorrhage (5.0%) and hypovolemic shock (1.3%). Mortality rate from abortion in Thailand during 2005 to 2009 is about 0.06-0.09%[1].

Surgical curettage is considered an effective treatment for incomplete abortion with only 1% failure rate. This procedure is recommended for gestational age lower than 15 weeks[2]. This life-saving procedure is easy to perform in many settings such as in an operating room or an outpatient office[3]. However, this procedure causes undesirable pain for which adequate anesthesia is needed. A number of methods for pain relief have been used, including intravenous sedation with meperidine, local anesthesia with paracervical block (PCB)[4, 5] and lidocaine spray in addition to PCB[6]. The patients who receive sedation with meperidine had more dizziness and nausea while the patients who receive PCB may experience more numbness[7]. While these methods have different adverse effects, evidence on which method is the most effective in pain relief remains inconclusive[7-9]. The primary objective of this study was to evaluate the efficacy of intravenous sedation, PCB and PCB plus lidocaine spray for pain relief during uterine curettage in first trimester incomplete abortion. The secondary objective was to evaluate adverse effects and satisfaction of the three methods.

Materials and Methods

This three-arm parallel-group randomized trial was conducted in Sanpasitthiprasong Hospital from July 2017 to August 2018 after approval of institutional ethical committee (048/2560). This project was registered at http://www.thaiclinicaltrials.gov (TCTR20180802002). All pregnant women, aged 15-45 years old who diagnosed incomplete abortion and required curettage at gestational age lower than 14 weeks were assessed for eligibility. The participants who had septic abortion, unstable vital signs, a history of hypersensitivity to lidocaine or meperidine, and those who were unable to communicate to evaluate pain score were excluded. After enrollment, the participants were randomized into 3 groups: Group 1 – to receive intravenous meperidine 50 mg and diazepam 10 mg and wait for 5 minutes before starting uterine curettage, Group 2 – to spray the cervix with 2 puffs of normal saline followed by PCB with 5 ml of 1% lidocaine solution using 23 gauge spinal needle at cervicovaginal junction 4 and 8 o'clock and wait for 2 minutes before starting the curettage, and Group 3 – to spray the cervix with 2 puffs of 10% lidocaine spray (20 mg) followed by PCB. Random numbers were computer-generated and put in opaque envelops. After written informed consent was given, an independent research staff opened the envelops according to the order that the participants enrolled into the study. Incomplete abortion was defined as bleeding that follows partial placental separation and dilation of the cervical os. Gestational age was calculated based on the date of the last menstrual period, in which there

was doubt, this gestational age was estimated by bimanual pelvic examination and/or an ultrasound examination. Standard uterine curettage procedure was performed in all participants. All participants were in lithotomy position. After cleaning of perineum with chlorhexidine solution, the speculum was inserted to expose the whole cervix. Pain relieving method was performed according to the assigned group. Anterior lip of the cervix was clamped at 2 and 10 o'clock with tenaculum. Sharp curettage was performed until uterine cry was heard. The tenaculum was removed, and then bleeding was checked and stopped. The speculum was removed. Doxycycline 100 mg oral twice daily was prescribed for 7 days in all participants.

Sample size was calculated by using the difference of mean pain score from previous study by Karasahin KE et al.[6] and Allen RH et al.[10] with power of 80% and a 2-sided type I error at 5%. With 10% addition for drop out, sample size per group was 55. Interim analysis was pre-planned at one year after recruitment.

Numerical rating scale (NRS) using to assess pain was defined as "0 is no pain" and "10 is the worst possible pain". Pain was evaluated at any point of time before, during, after procedure immediately and after procedure 30 minutes by the research staff who did not perform procedure. Data on adverse effects, requirement of additional intravenous analgesia, satisfaction to pain-relieving methods used during procedures, overall satisfaction, and length of hospital stay were recorded.

An intention-to-treat analysis was used with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were described using number (percentage), mean (standard deviation), and median (interquartile range). Comparisons in outcomes across the three treatment groups were performed using chi-square test, ANOVA and Kruskal-Wallis test for categorical, normally and non-normally distributed continuous variables respectively. Pairwise comparisons were done using chi-square test, student t test and Mann-Whitney-U test. A p-value of < 0.05 was considered statistically significant.

Results

During study period, there were 245 pregnant women presented with incomplete abortion and required curettage. After history review and physical examination, 9 cases were excluded due to unstable vital signs (n = 2), and septic abortion (n = 7). There were 115 pregnant women declined to participate. A pre-planned interim analysis at 12 months of enrollment showed that there was statistically significant different among treatment groups; therefore, the study was terminated. This resulted in a total of 121 pregnant women being enrolled and they were divided into three groups: 43 in the Intravenous sedation, 37 in the PCB and 41 in the PCB plus spray groups (Fig. 1).

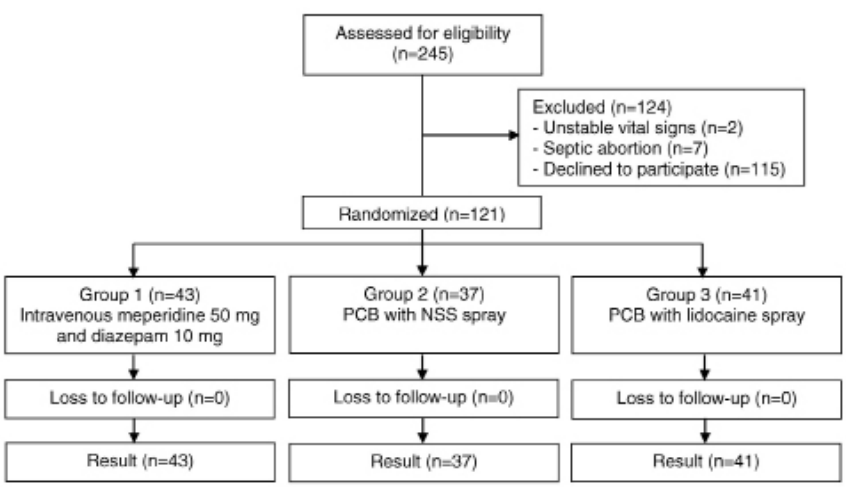

Fig. 1. Enrollment, randomization, and follow-up of the study participants.

The three treatment groups were similar regarding their age, gestational age at enrollment, parity, occupation, education, and body mass index (Table 1).

Table 1. Baseline characteristics of the pregnant women presented with first trimester incomplete abortion, overall and by treatment groups.

	Total (n=121)	Intravenous sedation (n=43)	Paracervical block (n=37)	Paracervical block plus lidocaine spray (n=41)	p value
Age	29 (24,37)	28 (24,37)	29 (21.5,37)	30 (26,36)	0.745
BMI	22.0 (19.1,25.6)	21.8 (18.0,25.0)	23.2(19.1,25.9)	21.6 (19.5,25.0)	0.308
Occupation					0.295
- Housewives	34 (28.1%)	11 (9.1%)	16 (13.2%)	7 (5.8%)	
- Employee	34 (28.1%)	12 (9.9%)	8 (6.6%)	14 (11.6%)	
- Student	7 (5.8%)	4 (3.3%)	2 (1.7%)	1 (0.8%)	
- Government officer	10 (8.3%)	3 (2.5%)	2 (1.7%)	5 (4.1%)	
- Farmer	11 (9.1%)	2 (1.7%)	4 (3.3%)	5 (4.1%)	
- Self-emplo	25 (20.7%)	11 (9.1%)	5 (4.1%)	9 (7.4%)	
Education					0.538
- Primary school	17 (14.0%)	5 (4.1%)	8 (6.6%)	4 (3.3%)	
- Secondary school	58 (47.9%)	20 (16.5%)	18 (14.9%)	20 (16.5%)	
- High Vocational Certificate	18 (14.9%)	7 (5.8%)	6 (5%)	5 (4.1%)	
- Bachelor's degree	24 (19.8%)	10 (8.3%)	5 (4.1%)	9 (7.4%)	
- Master's degree	4 (3.3%)	1 (0.8%)	0 (0%)	3 (2.5%)	
Underlying disease					0.518
- Diabetes mellitus	2 (1.7%)	0 (0%)	1 (0.8%)	1 (0.8%)	
- Thyroid disease	1 (0.8%)	0 (0%)	1 (0.8%)	0 (0%)	
- Hypertension	1 (0.8%)	1 (0.8%)	0 (0%)	0 (0%)	
- Others	1 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	
Gravidity	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,2)	0.030
Parity	1 (0,1)	10 (0,1)	1 (0,2)	1 (0,1)	0.340
Gestational age	10.3 (9.0,12.0)	10.7 (9.0,12.0)	10.0 (8.4,11.0)	10.4 (9.0,12.0)	0.165
Previous vaginal delivery	59 (48.8%)	23 (19%)	18 (14.9%)	18 (14.9%)	0.680
Previous uterine curettage	10 (8.3%)	6 (5%)	3 (2.5%)	1 (0.8%)	0.159
Prostaglandins used	41 (33.9%)	16 (13.1%)	10 (8.3%)	15 (12.4%)	0.571
Operators					0.061
- 1st year resident	23 (19.0%)	12 (27.9%)	5 (13.5%)	6 (14.6%)	
- 2nd year resident	75 (62.0%)	19 (44.2%)	27 (73.0%)	29 (70.8%)	
- 3rd year resident	23 (19.0%)	12 (27.9%)	5 (13.5%)	6 (14.6%)	

Note: Data in the table are given as or number (percentage) and median (interquartile range) for categorical and continuous variables respectively.

They were also similar according to medical history, including previous history of vaginal delivery, previous history of uterine curettage, history of prostaglandin use and underlying diseases. The only difference between the treatment groups was in gravidity and the difference was very small. Before receiving uterine curettage, participants in the three treatment groups reported similar pain scores (Table 2).

Comparison of pain scores across three treatment groups is shown in Table 2. Pain score during undertaking uterine curettage was significantly different across the three treatment groups (median score of 5 in Intravenous sedation group, 5 in PCB group, 4 in PCB plus spray group, p = 0.001). The differences in pain scores across the three treatment groups remained significant both at immediately and 30 minutes after therapeutic curettage (p = 0.025 and 0.003 respectively). Pairwise comparisons found the PCB plus spray group had a lower pain score during the therapeutic curettage than PCB (p = 0.001) and Intravenous sedation group (p = 0.002). Similar findings on pairwise comparison both at immediately and 30 minutes after therapeutic curettage were also observed.

Fig. 2. shows changes in pain scores at different time points by treatment groups. No additional intravenous analgesia was given in all treatment groups.

Table 2. Comparison of pain score among groups before, during, immediately and 30 minutes after uterine curettage.

	Total (n=121)	Intravenous sedation (n=43)	Paracervical block (n=37)	Paracervical block plus lidocaine spray (n=41)	p value
Before procedure	1 (0, 5)	0 (0, 5)	2 (0, 5)	0 (0, 3)	0.098
During procedure	5 (4, 7)	5 (5, 8)	5 (5, 7)	4 (3, 5)	0.001
		p = 0.800	p = 0.001		
		p = 0.002			
After immediately	2 (0, 4)	3 (1, 5)	2 (0, 5)	1 (0, 3)	0.025
		p = 0.144	p = 0.292		
		p = 0.006			
After 30 minutes	0 (0, 0)	0 (0, 2)	0 (0, 1)	0 (0, 0)	0.003
		p = 0.242	p = 0.020		
		p = 0.001			

Note: Values in the table are given as median (interquartile range) and Kruskal-Wallis test was used for comparison across treatment groups.

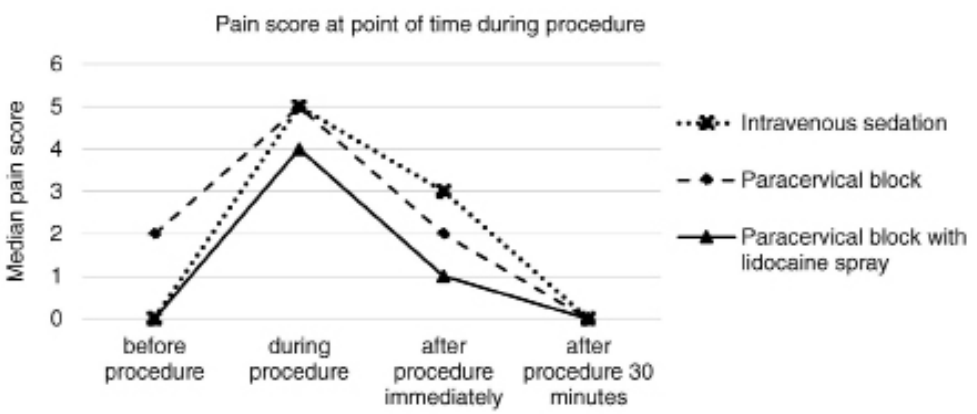

Fig. 2. Pain score at point of time during procedure.

Adverse effects and complications are shown in Table 3. Nausea and dizziness were significantly different across treatment groups, with the Intravenous sedation group reporting considerably more frequent than the other two groups ($p < 0.001$). Numbness was significantly different across treatment groups, with highest occurrence in the PCB group. There were a few participants having vomiting, tinnitus and feeling metallic taste, and there was no difference in these adverse effects between treatment groups. No serious complication such as uterine perforation was reported in either group.

Table 3. Comparison of adverse effects among treatment groups.

	Total (n=121)	Intravenous sedation (n=43)	Paracervical block (n=37)	Paracervical block plus lidocaine spray (n=41)	p value
Nausea	22 (18.2%)	17 (14.0%)	2 (1.7%)	3 (2.5%)	< 0.001
Vomiting	1 (0.8%)	1 (0.8%)	0 (0%)	0 (0%)	0.401
Dizziness	26 (21.5%)	20 (16.5%)	4 (3.3%)	2 (1.7%)	< 0.001
Tinnitus	7 (5.8%)	2 (1.7%)	3 (2.5%)	2 (1.7%)	0.767
Numbness	5 (4.1%)	0 (0%)	4 (3.3%)	1 (0.8%)	0.043
Metallic taste	1 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	0.374

Note: values in the table are given as number (percentage).

Overall satisfaction was not significantly different among the three treatment groups (Table 4). Satisfaction of pain-relieving methods significantly differed across treatment groups ($p = 0.010$). Unsatisfaction was exclusively reported in 3.3% of the participants in the Intravenous sedation group.

Table 4. Levels of overall and anesthesia-related satisfaction of participants in three treatment groups.

	Total (n=121)	Intravenous sedation (n=43)	Paracervical block (n=37)	Paracervical block plus lidocaine spray (n=41)	p value
For pain-relieving methods					0.01
- Unsatisfied	4 (3.3%)	4 (3.3%)	0 (0%)	0 (0%)	
- Neutral	6 (5%)	1 (0.8%)	1 (0.8%)	4 (3.3%)	
- Satisfied	55 (45.5%)	15 (12.4%)	24 (19.8%)	16 (13.2%)	
- Very satisfied	56 (46.3%)	23 (19%)	12 (9.9%)	21 (17.4%)	
Over all					0.15
- Unsatisfied	2 (1.7%)	2 (1.7%)	0 (0%)	0 (0%)	
- Neutral	7 (5.8%)	3 (2.5%)	1 (0.8%)	3 (2.5%)	
- Satisfied	55 (45.5%)	16 (13.2%)	23 (19.0%)	16 (13.2%)	
- Very satisfied	57 (47.1%)	22 (18.2%)	13 (10.7%)	22 (18.2%)	

Note: values in the table are given as number (percentage)

Discussion

In this three-arm parallel-group randomized control trial, PCB with lidocaine spray had higher efficacy in pain relief during, immediate and at 30 minutes after uterine curettage compared to PCB alone and intravenous sedation, with minimal adverse effects reported. From the patient perspectives, PCB plus lidocaine spray was among the most satisfactory anesthetic methods.

The different mechanisms to pain relief of intravenous sedation and PCB with and without lidocaine spray may explain our key results. In term of mechanisms to relieve pain during curettage procedure, intravenous opioid binds to opioid receptors in the central nervous system, inhibits ascending pain pathways, and alters the perception and response to pain. This central acting mechanism of intravenous sedation method causes adverse effects such as nausea, vomiting[10]. Paracervical block is another proven method of pain relief during this procedure[5]. The anesthetic mechanisms of lidocaine in paracervical block are mechanical distention of tissue and peripheral nerve block[11]. However, paracervical block alone may not provide adequate analgesia[12]. Our study clearly demonstrated efficacy of lidocaine spray added on PCB over PCB alone and intravenous sedation method in pain relief during and immediately after curettage procedure which support previous study[6]. Of note, it seems that local anesthetic methods are at least not inferior to systemic central-acting anesthetic methods in pain relief in uterine curettage, with suggestively reduced adverse effects.

PCB plus lidocaine spray has been reported to be effective in pain relief for patients receiving uterine curettage. A 4-arm double-blind randomized control trial by Aksoy H et al.[13] found significant difference in pain relief for intra-procedural and 30-minute post-procedural periods across treatment groups without reporting pairwise comparison between two groups. In contrast, in addition to differences in outcomes across the three treatment groups our study was able to demonstrate the beneficial effects of PCB plus lidocaine spray over PCB alone. This suggests that lidocaine spray might have some potential incremental benefits in pain relief for intrauterine operative procedures. However, such benefits have been inconsistently documented in previous literature. A previous trial examining the effect of lidocaine spray on pain relief during endometrial biopsy[14] compared to placebo normal saline spray found that lidocaine spray did not help reduce pain. This is different from our findings. This may be explained by the differential complexity and duration of the two procedures.

Many factors may affect pain during and after uterine curettage such as age, education, uterine position, gestational age, psychosocial, a history of prior vaginal delivery and operators of uterine curettage[15-17]. Since the design of this study was randomized control trial, the effects of these factors on study outcomes were cancelled out. This was clearly supported by comparable levels of these factors in the three treatment groups as demonstrated in Table 1.

In term of adverse outcomes, our study found significantly higher nausea and dizziness in intravenous sedation group than PCB groups, which is different from a previous study by Allen RH et al.[10] This may be explained by different drugs used for intravenous sedation between the two studies. Meperidine combined with diazepam used in our study is essentially more potent and have longer half-life than fentanyl, with or without midazolam for antiemetic effect in Allen's. However, the proportion of nausea was similar in both studies (14% in our study compared with 15.9% mild nausea and 4.5% severe nausea in previous study).

Our study showed lower levels of patient unsatisfaction than previous studies investigating benefits of intravenous or systemic sedation. In our study, only a small proportion of participants reported unsatisfaction in all treatment groups (3.3%, 0%, 0% in intravenous sedation, PCB, PCB plus spray group, respectively). A study in USA(10) found that considerably higher proportions of participants reported unsatisfaction during uterine curettage (5.8%, 24.3%,16.0% and 9.1% for the PCB alone, PCB plus sublingual lorazepam, PCB plus low-dose intravenous

sedation of fentanyl and midazolam and PCB plus moderate-dose intravenous sedation groups respectively). There may be a number of reasons for such the difference between the two studies. First, participants in the two studies may be different regarding a number of factors possibly affecting satisfaction outcomes such as a history of vaginal delivery, previous experience of uterine curettage. Significant proportion of participants in our study had experience of vaginal delivery (median parity of 2), and a previous history of uterine curettage (8.3%), while almost two-thirds of participants in the US study was nulliparous and half had bad impression from prior induced abortion. Additionally, different study designs may explain the disparity in satisfaction/ unsatisfaction levels between both studies. The US study was observational prospective study, while ours was randomized controlled trial. It is possible that participants in the trials were highly selected and different from those enrolled in observational studies regarding expectation and hence satisfaction.

Our study was a three-arm parallel-group randomized control trial with standardized outcomes ascertainment and intention-to-treat analysis. Together these allowed us to be able to control for possible confounding, and hence high study internal validity was achievable. This study was among the first to compare the effect of intravenous sedation with meperidine and diazepam to widely used anesthetic methods such as PCB. Comparable effects on pain relief of meperidine plus diazepam and PCB alone suggest potential use of meperidine plus diazepam instead of PCB alone in resource-constrained healthcare settings. However, our study has some limitations. First, blinding of patients and operators regarding treatment arms (PCB procedure and/or intravenous sedation) was not done in this study, so there might be the possibility of biases that the realization of these therapeutic procedures might have influenced physicians' performance and patients' responses on pain relief, adverse effects and satisfaction. It was also possible that adverse effects of meperidine and diazepam, particularly drowsiness and dizziness, may have effects on the ways that the participants felt and reported their pain levels.

Conclusion

PCB plus 10% lidocaine spray was effective in pain relief with fewer adverse effects for incomplete abortion uterine curettage procedure compared to PCB alone or intravenous sedation. This might suggest the potential use of a combined treatment of PCB plus lidocaine spray in these groups of patients.

Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Factors Associated with Lower Urinary Tract Symptoms in Thai Women with Uterine Leiomyomas

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ABSTRACT

Objectives: To identify the associated factors between uterine leiomyoma and lower urinary tract symptoms (LUTS) in Thai women.

Materials and Methods: One hundred and thirty eightwomen presenting with uterine leiomyoma at gynecologic out-patients clinic, King Chulalongkorn Memorial Hospital during August, 2014-March, 2015 were included. International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms Module (ICIQ-FLUTS) questionnaires were completed by all patients to identify the presence of LUTS. The LUTS case was defined by the present of any ICIQ-FLUTS questions score more than or equal to 2. The case: control ratio was 1:1. The controls were matched at the same day or within 3 days of the case. The patients' characteristics and the ultrasonographic data were collected.

Results: Among 138 leiomyoma patients were participated (69 cases and 69 controls). The mean age was 43.52 ± 7.4 and 44.86 ± 7.4 years respectively. There was no difference in body mass index and menopausal status. By univariate comparison, the mean of the total uterine volume and the largest leiomyoma volume were significantly different between groups. After the multivariate analysis, only the uterine volume more than 400 cm3 (odds ratio (95% confidence interval) = 2.44 (1.03-5.75)) and the largest leiomyoma volume more than 14 cm^3 (odds ratio (95% confidence interval) = 2.53 (1.02-6.37)) were significantly associated with LUTS.

Conclusion: Uterine volume ≥ 400 cm^3 and largest leiomyoma volume ≥ 14 cm^3 were the risk factors of LUTS in Thai women with leiomyoma.

Keywords: leiomyoma, uterine fibroid, lower urinary tract symptoms, LUTS, ICIQ-FLUTS.

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ปัจจัยที่เกี่ยวข้องกับอาการผิดปกติของทางเดินปัสสาวะส่วนล่างในสตรีไทยที่มีเนื้องอกของมดลูก

สุชาดา เอื้อจงมานี, สุวิทย์ บุณยะเวชชีวิน

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาถึงความสัมพันธ์ของปัจจัยในเนื้องอกมดลูกที่สามารถทำนายการเกิดอาการผิดปกติของอาการทางเดินปัสสาวะส่วนล่าง*

วัสดุและวิธีการ: *ทำการศึกษาในสตรีไทย 138 คน ที่มีเนื้องอกมดลูกที่มารับการรักษาที่คลินิกนรีเวชกรรม โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนสิงหาคม พ.ศ.2557 ถึง มีนาคม พ.ศ.2558 ผู้ป่วยจะทำการตอบแบบสอบถาม International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms Module (ICIQ – FLUTS) เพื่อสอบถามอาการทางเดินปัสสาวะส่วนล่าง โดยผู้ที่มีคะแนนของแบบสอบถามในข้อใดข้อหนึ่งมากกว่าหรือเท่ากับ 2 จะจัดอยู่ในกลุ่มที่มีอาการผิดปกติของทางเดินปัสสาวะส่วนล่าง โดยสัดส่วน case: control คือ 1:1. ทำการคัดเลือกกลุ่มควบคุมในวันเดียวกัน หรือไม่เกิน 3 วันจากวันที่คัดเลือกกลุ่มที่มีอาการทางเดินปัสสาวะส่วนล่าง พร้อมทั้งทำการบันทึกข้อมูลพื้นฐานของผู้ป่วยและผลการตรวจอัลตราซาวด์*

ผลการศึกษา: *มีจำนวยผู้ป่วยเนื้องอกมดลูก 138 ราย (กลุ่มที่มีอาการ 69 ราย และกลุ่มควบคุม 69 ราย) ค่าเฉลี่ยของอายุคือ 43.52 ± 7.4 และ 44.86 ± 7.4 ปี ตามลำดับ ไม่พบความแตกต่างของดัชนีมวลกาย และภาวะการหมดประจำเดือน จากการเปรียบเทียบแบบ univariate พบว่าค่าปริมาตรของมดลูก และปริมาตรของขนาดก้อนเนื้องอกที่ใหญ่สุด แตกต่างกัน จากการเปรียบเทียบแบบ multivariate พบว่า ค่าปริมาตรของมดลูกมากกว่า 400 ซม.^{3} (odds ratio (95% confidence interval) = 2.44 (1.03-5.75)) และปริมาตรของขนาดก้อนเนื้องอกที่ใหญ่ มากกว่า 14 ซม.^{3} (odds ratio (95% confidence interval) = 2.53 (1.02-6.37)) สัมพันธ์ต่อการเกิดอาการผิดปกติของทางเดินปัสสาวะส่วนล่าง*

สรุป: *จากการเปรียบเทียบแบบ multivariate พบว่า ค่าปริมาตรของมดลูกมากกว่า 400 ซม.^{3} (OR (95% CI) = 2.44 (1.03-5.75)) และปริมาตรของขนาดก้อนเนื้องอกที่ใหญ่ มากกว่า 14 ซม.^{3} (OR (95%CI) = 2.53 (1.02-6.37)) สัมพันธ์ต่อการเกิดอาการผิดปกติของทางเดินปัสสาวะส่วนล่าง*

คำสำคัญ: *เนื้องอก, เนื้องอกในมดลูก, อาการของทางเดินปัสสาวะส่วนล่าง, LUTS, ICIQ-FLUTS*

Introduction

Uterine leiomyoma is the most common benign tumor of smooth muscle of the uterus[1]. The exact prevalence of uterine leiomyoma is unknown. Estimate range is about 60-80 percent in African-American women, which higher than Caucasian women (40-70 percent)[2]. For Asian women, there was report of the overall prevalence of uterine leiomyoma up to 20 percent and about 40 percent was identified in women older than 40 years old[3]. In Thailand, the incidence of the leiomyoma in the total abdominal hysterectomy specimen was 60 % and 18.6 % were associated with adenomyosis[4].

Patients with uterine leiomyomas are usually detected incidentally without symptoms or with symptoms such as abnormal vaginal bleeding, pelvicpain, infertility[7-9], as well as the compressive symptoms which can be divided into two groups, 1) lower urinary tract symptoms (LUTS) such as urinary frequency, nocturia and 2) constipation or difficult defecation. There is evidence that the reduction in size of the uterine leiomyoma volume about 35% by uterine arteries embolization can reduce the symptom of urinary frequency up to 68%[5]. The reduction in size of uterine leiomyomas with GnRH can also decrease the urinary frequency, nocturia and urgency[6]. These evidences suggest the association between uterine size and LUTS. However, there are few reports that specified the details of leiomyoma and the correlations to the LUTS[5, 8], and there is no study about the leiomyoma factors used to predict the presence of LUTS. The aim of this study is to identify factors of uterine leiomyoma and its association to the LUTS in Thai women.

Materials and Methods

A case-control study designed was conducted. After the IRB approval, 138 Thai women who were diagnosed as having uterine leiomyoma by pelvic examination and ultrasonography at Gynecologic clinic at King Chulalongkorn Memorial Hospital (KCMH) during August 2014-March 2015 were recruited. Inclusion criteria were women age 18 and older who diagnosed as having the uterine leiomyoma by clinical symptoms, pelvic examination and ultrasonography. The exclusion were pregnancy, diagnosis of the other concurrent pelvic mass, history or current gynecologic malignancy, history and treatment of a lower urinary tract disorders, chronic urinary tract infection, pelvic organ prolapse, history of pelvic radiation or endocrine disease that can cause polyuria (such as diabetes mellitus, diabetes insipidus). The criteria of leiomyoma diagnosed by ultrasonography were: presence of the well defined, focal masses and solid hypoechoic with posterior acoustic shadowing[10]. The transvaginal or transabdominal ultrasonographic data were collected from the outpatient record (OPD card) if the ultrasonographies were performed within 6 months before recruitment. If not, the ultrasonography was performed at the recruitment day. The total uterine volume, leiomyoma location, size, and number were recorded. Volume of uterus and largest leiomyoma were calculated using the formula for an ellipsoid shape (volume = 0.5236 x length x width x height) and recorded in cubic centimeters (cm^3)[11]. Location of uterine leiomyoma was grouped as anterior, posterior and others. The LUTS were diagnosed as the recommended definition by the International continence society (ICS) terminology[12]. These included eight symptoms (nocturia, urgency, frequency, stress urinary incontinence, urge incontinence, straining, difficulty emptying bladder and delayed urine flow)[12].

LUTS cases were identified by the International Consultation on Incontinence-Female Lower Urinary Tract Symptoms Module questionnaire (ICIQ – FLUTS)[13]. TheThai versions of the ICIQ – FLUTS questionnaires were completed by all patients. The ICIQ-F LUTS (Thai version) was already test for reliability and validity (test retest reliability = 0.8, Alpha cronbach = 0.9) from our pilot study in 130 cases. This questionnaire contained 13 questions. The LUTS cases were defined by the present of any ICIQ-FLUTS questions score equal or more than 2. All cases with LUTS were asked to perform the 3 days voiding diary to confirm the presence of LUTS. The case:control ratio was 1:1. The controls were selected as the next

available after each case recruitment at the same day or within 3 days of the cases. The nocturia, urgency, and urinary frequency were confirmed by voiding diary as these following characteristics according to the ICS definition[12].

Nocturia: presence of night time urination more than one.

Urgency: presence of uninhibited or delayed feeling to void at least 1 episode of urgency with or without incontinence in 3 days.

Urinary frequency: presence of more than 8 times urination per day.

The patients' characteristics and the ultrasonographic data were collected at the day of recruitment. The sample size calculation was done using the previous data of the factors of the uterine size more than 400 cm^3 that related to LUTS (OR= 3.3) from the previous study of Christina et al[14]. With the significant level less than or equal to 0.05, power of 80%, case per control ratio of 1:1. The sample size per group was 69 cases per group.

For statistical analysis, using SPSS version 17.0 with independent t test and a Mann Whitney U test for continuous data and Chi squared test for categorical data. And then multiple logistic regressions were used for odd ratio calculation.

Results

There was no significant difference between demographic data in both groups (Table 1). The median (Interquartile range: IQR) was used for data presentation as the data was not normally distributed. We found that the LUTS in our study comprised of nocturia 42 cases (60.86%), difficult emptying bladder 36 cases (52.2%), urinary urgency 31 cases (44.9%), urinary frequency 17 cases (24.6%), delayed urine flow 9 cases (13.0%),stress urinary incontinence 8 cases (11.5%), urge urinary incontinence 6 cases (8.6%), and straining 6 cases (8.6%).

For leiomyoma factors, the median (IQR) of uterine volume in LUTS group was statistically significant higher than control group (263.33 (137.28-538.87) versus 142.02(83.59-283.29) (Table 2). The median (IQR) of the largest leiomyoma volume (cm^3) in LUTS group was also significantly higher than control group (103.44 (33.05-286.82) versus 49.85 (9.55-125.61) (Table 2). The location, type and number of leiomyoma were not significantly different in both group (Table 2). By using multivariate logistic regression analysis, the uterine volume ≥ 400 cm^3 and largest leiomyoma volume ≥ 14 cm^3, odd ratio (95% CI) = 2.44 (1.03-5.75) and 2.53 (1.02-6.37) respectively, were the significant factors of LUTS (Table 3).

Table 1. Demographic data.

	LUTS group (N = 69)	No LUTS group (N = 69)	p value
Mean ± SD			
Age (years)	43.52 ± 7.4	44.86 ± 7.4	0.855
BMI (kg/m^2)	24.76 ± 3.1	23.84 ± 4.14	0.454
Premenopause	60 (86.95 %)	58 (84.05 %)	0.854
Postmenopause	9 (13.04 %)	11 (15.94 %)	0.655
Parity	1 (0-4)	0 (0-4)	0.728
Delivery route			
- Vaginal	0 (0-4)	0 (0-4)	0.333
- Cesarean	0 (0-2)	0 (0-2)	0.533
n (%)			
History of pelvic surgery	6 (8.69)	6 (8.69)	1.000

Table 2. Univariate analysis of the Leiomyoma factors.

	LUTS group (N = 69)	No LUTS group (N = 69)	p value
Median (IQR)			
Uterine volume (cm^3)	263.33 (137.28-538.87)	142.02 (83.59-283.29)	0.001*
Largest leiomyoma volume (cm^3)	103.44 (33.05-286.82)	49.85 (9.55-125.61)	0.001*
n (%)			
Number of myoma			
- One	37 (53.62 %)	38 (55.10 %)	0.816
- Two	14 (20.30 %)	11 (15.09%)	0.549
- Three or more	18 (26.10 %)	20 (29.00 %)	0.746
Type of largest myoma			
- Submucous	1 (1.40 %)	2 (2.90 %)	0.564
- Intramural	46 (66.70 %)	48 (69.60 %)	0.837
- Subserous	22 (31.90 %)	19 (27.50 %)	0.639
Location of myoma			
- Anterior	23 (33.30 %)	22 (31.90 %)	0.881
- Posterior	19 (27.50 %)	24 (34.80 %)	0.446
- Other	27 (39.10 %)	23 (33.30 %)	0.572

Table 3. Multivariate analysis of the Leiomyoma factors.

	Odds ratio	95% CI	p value
Uterine volume ≥ 400 cm^3	2.44	(1.03-5.75)	0.04
Largest leiomyoma volume ≥ 14 cm^3	2.53	(1.02-6.37)	0.04

Discussion

Lower urinary tract symptoms are common presenting symptom of uterine leiomyoma, and are one of the indications for treatment. Not all women with leiomyoma presents with LUTS. There are few studies report about the relationship between any lower urinary tracts symptom and leiomyoma[14-18]. There were reports of the cut off level of more than 12 weeks size uterus[14] and largest diameter of leiomyoma nodule of 3 cm^3[17] related to the LUTS in women with leiomyoma uteri. But there is no study defining the risk factors for predicting LUTS symptoms in women with leiomyoma. Our study is the first case-control study that established the leiomyoma factors that can predict the LUTS. We found that the total uterine volume more than 400 cm^3 and largest leiomyoma volume of greater than 14 cm^3 significantly affect the symptoms of lower urinary tract. The reason that we

choose these cut off value, the uterine volume of 400 cm^3, came from the evidence of the study of Goldstein et al[11] (the uterine 12 weeks of gestation had the uterine volume equivalent to 383±29 cm^3[11], so we choose the round number of 400 cm^3 to be the cut off level. And the cut off volume of the largest leiomyoma nodule of 14 cm^3 came from the approximation calculation of the leiomyoma nodule with diameter of 3 cm^3 (the ellipsoidal shape volume formula calculation). We believe that the volume calculation form three dimension measurement is more reliable than using only one dimension to be the cut off value.

Our finding is similar to prior study that reported the uterine size greater than 12 weeks sizes affect LUTS[14]. We found that the number of leiomyoma, type and location of the tumor don't affect on any symptoms of the urinary system. This differs from the study of Candace et al that report of the anterior location of the dominant uterine fibroid was associated with worsening voiding dysfunction[17]. The results from our study can help physicians select the cases that are at the higher chance of developing the LUTS and plan for close follow up of the lower urinary tract symptoms. Moreover these finding are useful information for counseling in leiomyoma patients who are concerned about the risk of developing the LUTS. This study can help giving more information for physicians for taking care of patients in Thai women with leiomyoma.

The strengths of this study – this is the first case control study to identify the factors of uterine leiomyoma and the association to the lower urinary tract symptom. We used the standard questionnaire, ICIQ-FLUTS, to diagnose lower urinary tract symptoms and use the 3 days voiding diary for confirmation. Our study has no time bias because the data from both group were collected at the same or similar period of the sample recruitment.

However, our study focuses at the leiomyoma factors that can have the effect on urinary symptoms. Some other non-leiomyoma factors are not included in this study. For other limitation, we collected patients' data from the outpatient record (OPD card) with inclusion criteria that the ultrasonographies had to perform within 6 months before recruitment. This may cause some deviated of data due to multiple investigator and duration from latest ultrasound. Further study to find out the other non-leiomyoma factors that may be the risk factors for LUTS in Thai women is advocated.

Conclusion

We found total uterine volume more than 400 cm^3 and largest leiomyoma volume greater than 14 cm^3 associated with the lower urinary tract symptoms.

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Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Knowledge and Attitude of Pregnant Women Undergoing Cell-free DNA Screening at the King Chulalongkorn Memorial Hospital

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ABSTRACT

Objectives: To investigate the knowledge and attitude of pregnant women before undergoing cell-free DNA screening at King Chulalongkorn Memorial Hospital (KCMH).

Materials and Methods: A cross-sectional study recruited 400 singleton pregnant women who underwent cell-free DNA screening at KCMH from December 2016 to August 2017. Self-administered questionnaires were used to evaluate participants' knowledge and attitude.

Results: Four-hundred pregnant women answered the questionnaires and 344 responses were considered valid. The maternal age ranged from 23 to 46 years and mean age was 34.8 ± 3.6 years. Almost all of the participants answered correctly about the test's ability to detect trisomy 21, trisomy 18, trisomy 13, and fetal sex (96.8, 83.7, 84.8, and 93.9% respectively). Eighty-nine percent of the women answered correctly about the time to start cell-free DNA testing, and 68% answered correctly about detection rate of trisomy 21. Some participants had misconceptions about the test's ability such as false negative rate, thalassemia screening, fetal malignancy detection, autistic detection, cleft lip-cleft palate detection, and the option of termination of pregnancy if the screening was positive. Seventy-nine percent were aware of the possibility of re-sampling. Additional data showed that participants had positive attitude towards cell-free DNA screening, and preferred to use it again for future pregnancy.

Conclusion: Our study showed that the majority of the participants had good knowledge of the test's ability to detect trisomy, and a possibility of re-sampling. However, almost half of the participants misunderstood that it could detect all genetic abnormalities. This study showed the magnitude of expectations and misunderstandings about cell-free DNA screening.

Keywords: cell-free DNA, NIPT, singleton, knowledge, attitude

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ความรู้และทัศนคติของหญิงตั้งครรภ์ที่เข้ารับการตรวจกรองโดยวิธีเซลล์ฟรีดีเอ็นเอในโรงพยาบาลจุฬาลงกรณ์

พัชราภรณ์ ชโลปกรณ์, ศักนัน มะโนทัย

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินความรู้และทัศนคติของหญิงตั้งครรภ์ก่อนเข้ารับการตรวจคัดกรองเซลล์ฟรีดีเอ็นเอที่โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย*

วัสดุและวิธีการ: *เป็นการศึกษาภาคตัดขวาง โดยเลือกกลุ่มตัวอย่างจากหญิงตั้งครรภ์เดี่ยวจำนวน 400 คน ที่จะเข้ารับการตรวจคัดกรองเซลล์ฟรีดีเอ็นเอในโรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย ในช่วงเดือนธันวาคม พ.ศ.2559 ถึงเดือนสิงหาคม พ.ศ.2560 โดยใช้แบบสอบถามในการประเมินความรู้และทัศนคติของหญิงตั้งครรภ์ก่อนได้รับคำปรึกษาทางพันธุกรรม*

ผลการศึกษา: *หญิงตั้งครรภ์ 400 คน ตอบแบบสอบถาม โดยมีผู้ตอบแบบสอบถามครบถ้วนจำนวน 344 คน อายุอยู่ระหว่าง 23 ถึง 46 ปี โดยมีอายุเฉลี่ย 34.8 ± 3.6 ปี ผู้เข้าร่วมงานวิจัยเกือบทั้งหมดตอบถูกเกี่ยวกับความสามารถในการตรวจหา trisomy 21, trisomy 18, trisomy 13 และเพศของทารก (ร้อยละ 96.8, 83.7, 84.8 และ 93.8 ตามลำดับ) ร้อยละ 89 ของผู้เข้าร่วมวิจัย ตอบถูกเกี่ยวกับเวลาในการเริ่มการตรวจเซลล์ฟรีดีเอ็นเอ และร้อยละ 68 ตอบถูกเกี่ยวกับอัตราการตรวจหา trisomy 21 ผู้เข้าร่วมงานวิจัยส่วนหนึ่งยังมีความเข้าใจผิดเกี่ยวกับการทดสอบ เช่น อัตราการเกิดผลลบลวง, การตรวจคัดกรองธาลัสซีเมีย, การตรวจพบมะเร็งในทารก, การตรวจพบออทิสติก, การตรวจพบปากแหว่งเพดานโหว่ และการตัดสินใจยุติการตั้งครรภ์ หากผลการคัดกรองเป็นบวก ร้อยละ 79 ทราบว่าอาจมีโอกาสที่ต้องเจาะเลือดซ้ำ ในด้านทัศนคติต่อการตรวจเซลล์ฟรีดีเอ็นเอ ผู้เข้าร่วมงานวิจัยมีความพึงพอใจสูงต่อการทดสอบนี้ และมีแนวโน้มที่จะเลือกใช้ตรวจคัดกรองในครรภ์ถัดไป*

สรุป: *หญิงตั้งครรภ์ส่วนใหญ่มีความรู้เกี่ยวกับความสามารถของการทดสอบในด้านการตรวจหา trisomy และเข้าใจว่ามีโอกาสที่จะต้องถูกเก็บตัวอย่างเลือดซ้ำ อย่างไรก็ตามเกือบครึ่งหนึ่งของผู้เข้าร่วมงานวิจัยยังเข้าใจผิดว่าการทดสอบนี้สามารถตรวจพบความผิดปกติทางพันธุกรรมทั้งหมดได้ซึ่งแสดงให้เห็นว่า ผู้เข้าร่วมงานวิจัยมีความคาดหวังที่เกินจริง และยังมีความเข้าใจผิดเกี่ยวกับการตรวจคัดกรองเซลล์ฟรีดีเอ็นเอ การศึกษานี้สะท้อนให้เห็นถึงความสำคัญของการให้ความรู้ที่ถูกต้องในด้านความสามารถของการตรวจคัดกรองนี้ เพื่อให้เกิดความเข้าใจที่ถูกต้องต่อไป*

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Introduction

Nowadays, fetal chromosome abnormalities are seen as a major global problem. The most common chromosome disorder of live birth infants is Down syndrome. The prevalence increases as the maternal age increases[1,2]. A reference from CDC from 1979 to 2003 showed that the prevalence of Down syndrome increased up to 30% in the United States from 9.0 to 11.8 per 100,000 live births[3]. The prevalence of Down syndrome in Thailand also increased from 1 in 800 to 1 in 526[4]. This problem is considered to be significant because it affects the family and the society. Children with Down syndrome have delayed physical development and mental retardation. The Study of Health Intervention and Technology Assessment Program (HITAP) in 2011 estimated the lifelong cost of Down syndrome to be around 2,500,000 baht per person of which 40% are related to medical issues[5].

Prenatal screening technology was developed to detect genetic disorders. The conventional screenings consist of maternal age older than 35 years, ultrasound and biochemical markers in maternal serum. The detection rate varies between 30% to 94%. False positive rate is 5-10% and positive predictive value (PPV) is only 1-3%. Therefore, more than 95% of pregnant women would undergo unnecessary invasive prenatal diagnosis such as amniocentesis, and chorionic villi sampling which can result in procedure related complications. Important complications such as chorioamnionitis (0.1%), amniotic fluid leakage (2%), and miscarriage (0.5-1%) may occur when such invasive procedures are performed[6]. However, in 1997, circulating fetal cell-free DNA discovered by Dennis Lo was developed to be a noninvasive screening procedure. This technique was based on the knowledge that maternal serum contains fragments of DNA, a small proportion of which derives from placental cell apoptosis. In 2011, this new prenatal screening technology is called cell-free DNA noninvasive prenatal testing (NIPT)[7-9].

Cell-free DNA screening can be performed at as early as the 10th week of gestation. The detection rate of Down syndrome is 99%, false positive rate is less than 1% and PPV is 70-90%[10]. It is obvious that cell-free DNA screening can reduce the need for invasive procedure which is associated with miscarriage and infection risks[11]. Moreover, this test can be used to screen fetal trisomy 18, trisomy 13, other chromosomal aneuploidies, monosomy X and other sex chromosomal aneuploidies. The American College of Obstetricians and Gynecologists (ACOG) in 2015 recommended that pregnant women may choose cell- free DNA for screening regardless of their aneuploidy risks[12]. However, they should understand the limitations of this test to avoid over expectation because it does not truly provide absolute diagnosis. A positive result must undergo diagnostic test to confirm fetal genetic disorder.

Previous studies have shown that there was a difference in the knowledge and attitude towards cell-free DNA screenings. In Hong Kong, 70-90% of the pregnant women who tested positive by another aneuploidy screening had high knowledge about cell-free DNA screening's efficacy and limitations with positive attitude towards the test[13,14]. In contrast, only 30% of Japanese pregnant women knew the sensitivity and weakness of this test[15].

In Thailand, NIPT became available in July 2012 which attracted a lot of attention[16]. However there are no studies or data available regarding the knowledge and attitude towards cell-free DNA screening in Thailand. Our study investigated the knowledge and attitude of pregnant women undergoing cell-free DNA screening at the King Chulalongkorn Memorial Hospital (KCMH).

Materials and Methods

Study design and participants

This cross-sectional study recruited 400 pregnant women who were about to undergo cell-free DNA at the Division of Maternal-Fetal Medicine (MFM), King Chulalongkorn Memorial Hospital. Sample size was calculated from proportion of cell-free DNA knowledge at 0.7[13] and number of required participants was 323. We estimated that incomplete questionnaire responses would be approximately 20%. Singleton pregnant women who were more than 18 years old and had

gestational age of more than 10 weeks were enrolled into the study. Pregnant women with a multifetal pregnancy or who were illiterate were excluded from the study. The primary objective was to evaluate the knowledge of cell-free DNA screening in pregnant women undergoing this test at the KCMH. The secondary objective was to evaluate their attitude towards the test.

Data collection and tools

The questionnaire was developed by by one of the authors in Thailand validated by 3 maternal-fetal medicine specialists. The reliability of the test was calculated by Cronbach's Alpha. The questionnaire was administered to pregnant women who requested cell-free DNA screening prior to the routine pretest counseling. A rapid response questionnaire consisted of 5 pages, and was separated into 3 sections which were designed to assess demographic data, knowledge and attitude on cell-free DNA screening. The demographic section collected the following information: age, race, religion, education, career, address, underlying diseases, obstetric history and problems in previous pregnancies. The knowledge part assessed the participants' understanding of the test's ability, its detection rate, its limitations, concept of the screening test, and source of information on cell-free DNA screening. This part consisted of fill-in-the-blank questions and true-false questions. The attitude part asked the participants why they chose to do cell-free DNA screening, what they would do if the test yielded positive result and their satisfaction of doing the cell-free DNA screening. The attitudes toward having an abnormal test result were scored using a five-point Likert scale ranging from 1 to 5; 5 being the most concerned to 1 being unconcerned. Also, the satisfaction towards cell-free DNA screening test at the KCMH was scored using a five-point Likert scale ranging from 1 to 5; 5 being very satisfied to 1 being very dissatisfied. A score of 4 or more indicated that the participant had a positive attitude towards cell-free DNA screening. The participants completed the questionnaire before pretest counseling.

Statistics analysis

Data were statistically analyzed using SPSS for Windows version 22. Descriptive statistics were used to calculate proportions. The differences between two groups were calculated by Chi-square tests or Fisher's Exact test where appropriate. The statistical significance was set at p-value of less than 0.05.

Ethical considerations

The study protocol and the questionnaires were approved by the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all women prior to recruiting them into the study.

Results

1. Demographic data:

Four-hundred pregnant women who underwent cell-free DNA screening at the KCMH from December 2016 to August 2017 answered the questionnaires. The reliability of the test by Cronbach's Alpha was 0.702. From 400 responses, 344 were considered valid. Fourteen percent (56/400) of the questionnaires were considered to be incomplete, and were excluded from the analysis. All participants were Thai. Most of the participants lived in the central part of Thailand. Seventy-four percent (256/344) lived in Bangkok. The demographic data are summarized in Table 1. The maternal age ranged from 23 to 46 years and the mean age was 34.8±3.6 years. Ninety-six percent of the participants had bachelor degree or higher education level. The obstetric history showed that 50.6% of the participants were primigravida most of whom were younger than 35 years old. Two women (0.6%) out of 344 participants had an abnormal child in a previous pregnancy; one child had Down syndrome and the other child had undescended testis. One point seven percent of the participants had an individual with Down syndrome in their families. Two percent had another prenatal screening before this present study; four women had a first trimester screening, one woman had a triple screen test and two women had a quadruple screen test.

Table 1. Demographic data of the participants undergoing cell-free DNA screening.

Demographic data	Total (%) N = 344	Age < 35 y (%) N = 149	Age ≥ 35 y (%) N = 195
Age (mean ± SD)	34.82 ± 3.581	31.61 ± 2.503	37.28 ± 1.978
BMI (mean ± SD)	22.11 ± 3.232	21.54 ± 3.161	22.54 ± 3.227
Race			
Thai	344 (100)	149 (100)	195 (100)
Region			
Central	310 (90.1)	140 (94.0)	170 (87.2)
North	6 (1.7)	0 (0)	6 (3.1)
South	3 (0.9)	2 (1.3)	1 (0.5)
East	17 (4.9)	6 (4.0)	11 (5.6)
West	1 (0.3)	0 (0)	1 (0.5)
Northeastern	7 (2.0)	1 (0.7)	6 (3.1)
Religion			
Buddhism	334 (97.1)	149 (100)	185 (94.9)
Christianity	3 (0.9)	0 (0)	3 (1.5)
Islam	5 (1.5)	0 (0)	5 (2.6)
Others	2 (0.6)	0 (0)	2 (1.0)
Education			
< Bachelor	13 (3.8)	6 (4.0)	7 (3.6)
Bachelor	234 (68.0)	104 (69.8)	130 (66.7)
> Bachelor	97 (28.2)	39 (26.2)	58 (29.7)
Career			
Government	57 (16.6)	26 (17.4)	31 (15.9)
Officer	144 (41.9)	70 (47.0)	74 (37.9)
Employee	3 (0.9)	0 (0)	3 (1.5)
No occupation	20 (5.8)	8 (5.4)	12 (6.2)
Business	59 (17.2)	28 (18.8)	31 (15.9)
Others	61 (17.7)	17 (11.4)	44 (22.6)
Gravida			
1	174 (50.6)	91 (61.1)	83 (42.6)
>1	170 (49.4)	58 (38.9)	112 (57.4)
Abortion			
No	274 (79.7)	124 (83.2)	150 (76.9)
Yes	70 (20.3)	25 (16.8)	45 (23.1)
Abnormal Children			
No	342 (99.4)	148 (99.3)	194 (99.5)
Yes	2 (0.6)	1 (0.7)	1 (0.5)
Medical Complication			
No	340 (98.8)	149 (100)	191 (97.9)
Yes	4 (1.2)	0 (0)	4 (2.1)

2. Knowledge about cell-free DNA screening

This study showed that pregnant women who underwent cell-free DNA screening at the KCMH knew about the test's ability to screen for trisomy 13 (84.9%), trisomy 18 (83.7%), trisomy 21 (96.8%), and fetal sex chromosome (93.9%). The majority of the participants knew that it was necessary to continue testing with an invasive diagnosis procedure (79.9%) if the screening result was positive and also, 79.1% percent of the women were aware that there was a chance of re-sampling for screening. The majority of the participants answered correctly about the sensitivity of the test and the earliest time to perform the test. However, less than 30% of the participants knew that the currently available test could not be used to screen for all chromosome disorders and other fetal anomalies such as thalassemia, autism, cleft lip and cleft palate. Only a minority knew that the test had a chance of false positive and false negative results. One-fourth (25%) misunderstood that after a positive cell-free DNA screening result, there was no need for confirmation test before terminating the pregnancy. Most of the participants obtained information about cell-free DNA screening from the internet, their primary doctors and friends. Data regarding the participants' knowledge are summarized in Tables 2 and 3.

Table 2. Knowledge of cell-free DNA screening in pregnant women undergoing cell-free DNA.

Correct answer of cell-free DNA test's ability	Total (%) N = 344	Age < 35 y (%) N = 149	Age ≥ 35 y (%) N = 195	p value
Down syndrome	333 (96.8)	142 (95.3)	191 (97.9)	0.167
Trisomy 13	292 (84.9)	137 (91.9)	155 (79.5)	0.001
Trisomy 18	288 (83.7)	132 (88.6)	156 (80.0)	0.032
Sex	323 (93.9)	141 (94.6)	182 (93.3)	0.618
All chromosome disorders	55 (16.0)	28 (18.8)	27 (13.8)	0.215
Blood group	68 (19.8)	33 (22.1)	35 (17.9)	0.333
Thalassemia	64 (18.6)	30 (20.1)	34 (17.4)	0.524
Cancer	113 (32.8)	56 (37.6)	57 (29.2)	0.102
Autistic child	73 (21.2)	47 (31.5)	26 (13.3)	< 0.0001
Cleft lip and cleft palate	97 (28.2)	48 (32.2)	49 (25.1)	0.148

Table 3. Knowledge of cell-free DNA test's abilities in pregnant women undergoing cell-free DNA.

Cell-free DNA	Total (%) N = 344
can be performed at as early as on the 10th week of gestation	306 (89.0)
has a sensitivity around 99%	233 (67.7)
there is a chance to have false positive (< 1%)	170 (49.4)
there is a chance to have false negative	92 (26.7)
is a screening test and need to have invasive diagnostic test	275 (79.9)
cannot terminate pregnancy if the result of the cell-free DNA is positive	258(75.0)
may need resampling	272 (79.1)

3. Attitudes toward cell-free DNA screening

Fig. 1. shows that the top three personal reasons to undergo cell-free DNA screening test were advanced maternal age, concern of complications of invasive diagnostic test, and concern of pain from the invasive test. Fifty-five point two percent of the participants were "most concerned" (had a score of 5) and 40.1% were "concerned" (had a score of 4) about receiving a positive result from the cell-free DNA screening. Seventy-six percent of the participants would decide to perform further invasive diagnosis test (i.e., amniocentesis) if the result of the cell-free DNA screening test was positive. Seventy-seven point six percent of the participants would terminate the pregnancy if the fetus was confirmed with Down syndrome (Fig. 2). Thirty-eight point seven percent of the participants were very satisfied (had a score of 5) and 53.2% of the participants were satisfied (had a score of 4) to have cell-free DNA screening (Fig. 3). Overall, most of the participants had a positive attitude towards cell-free DNA screening in the current and later pregnancies.

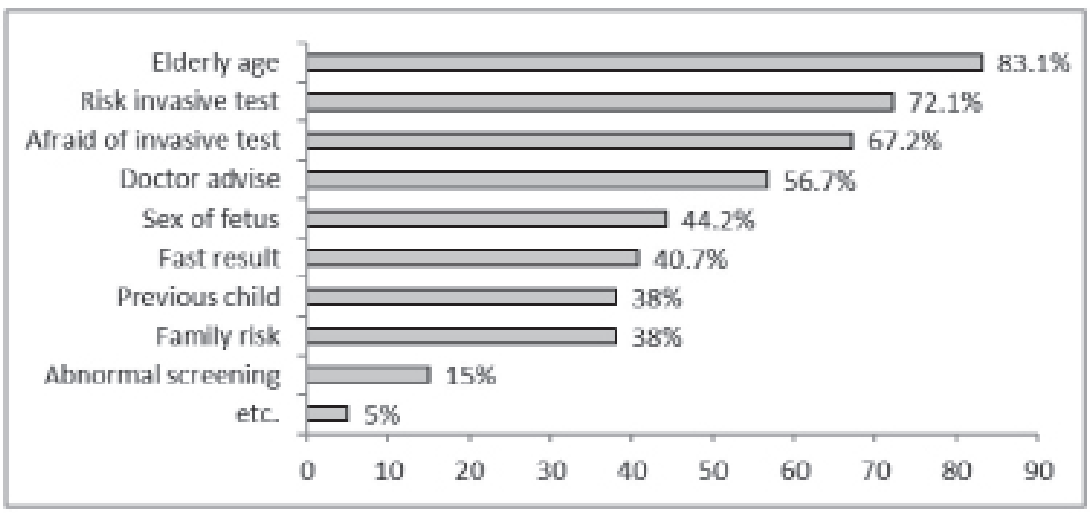

Fig. 1. Reasons to have cell-free DNA screening at the KCMH.

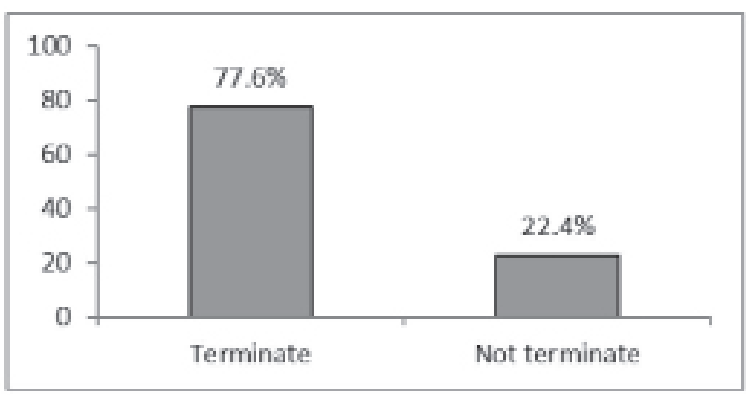

Fig. 2. Attitude towards positive prenatal diagnosis of Down syndrome to terminate pregnancy.

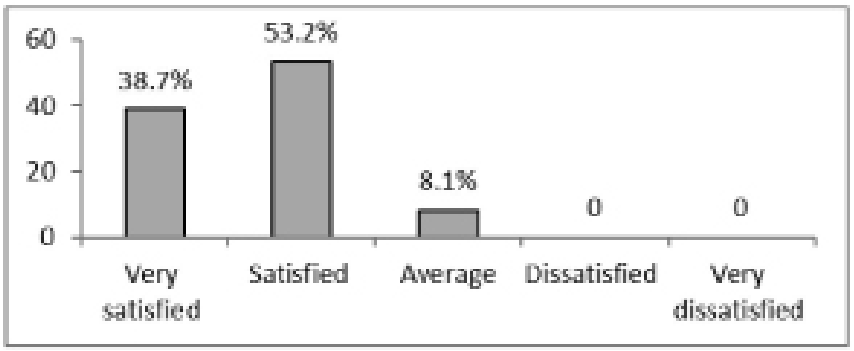

Fig. 3. Participants' satisfaction level of the cell- free DNA screening test at the KCMH.

Discussion

ACOG currently recommends offering cell-free DNA screening to high risk pregnant women, but also suggests that any woman may choose cell-free DNA screening. In this study, 43.31% of the participants undergoing cell-free DNA screening were in the low-risk group (age less than 35 years). This shows that cell-free DNA screening is widely accepted in low-risk women in Thailand.

A previous study from Japan which was conducted in 2015 reported that 75% of the participants knew that cell-free DNA screening can be used for screening Down syndrome but they did not know the test's ability to screen for trisomy 13 and trisomy 18[15]. For this study, more than 80% knew that the test can screen for trisomy 13, trisomy 18, trisomy 21 and fetal sex chromosome. This is likely due to the difference in population group between pregnant women in Japan and Thai pregnant women who sought cell-free DNA screening at KCMH.

The participants in this study had good knowledge of the test's detection rate which is similar to the study conducted in Hong Kong in 2015[13]. However, less than half of the participants in this study knew that the test could yield false positive and false negative results. Moreover, many of the participants at the KCMH seemed to have over expectation about the test's ability to screen for all chromosomal and other fetal abnormalities such as thalassemia, autism and so on. Previous studies showed that the knowledge of cell-free DNA screening of the pregnant women were based on the following factors: age, educational level, and interest in cell-free DNA screening[13-15,17]. In this study, we found that women in the younger age group had a better knowledge than the older age group about the test's ability to screen for trisomy 13 and trisomy 18.

This study is the first of its kind to assess the knowledge and attitude of pregnant women undergoing cell-free DNA screening in Thailand. There are several limitations in this study. Firstly, it is a descriptive study which was performed at a single center (KCMH). Thus, it may not represent the entire Thai population. Secondly, this study did not have the primary aim for subgroup comparison, so the result of subgroup analysis must be interpreted carefully.

Additional studies are needed to analyze the factors that affect the knowledge and attitudes in a study with a larger sample size.

Conclusion

In conclusion, our participants had good knowledge about the test's ability and had positive attitude towards cell-free DNA screening. However, there were some over expectation[18-20]. Additional study should provide the right information at the pretest counseling and evaluate whether it can improve the education and expectations in pregnant women undergoing cell-free DNA or not.

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Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

The Reliability of Transabdominal Cervical Length Measurement Compared with Transvaginal Measurement at 16-24 Weeks of Gestation

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ABSTRACT

Objectives: To determine reliability of transabdominal cervical length (TACL) compared with transvaginal cervical length (TVCL) at 16-24 weeks of gestation.

Materials and Methods: A prospective study was conducted in the Obstetrics and Gynecology Department at Phramongkutklao Hospital between 27 March 2017 and 29 December 2017. Singleton pregnant women who underwent ultrasound between 16-24 weeks of gestation with any indication were enrolled. Women with a history of cervical surgery, uterine contractions and vaginal bleeding were excluded. After voiding, TACL was measured followed by TVCL as per the protocols stipulated by the Fetal Medicine Foundation (2014). Demographic and medical data were collected. Cervical length measurements from both methods were compared, and the factors accounting for differences in measured lengths were considered.

Results: One hundred and forty-two women with singleton pregnancies agreed to participate in the study. Satisfactory TACL images could not be obtained within 5 min in 12 (8.6%) of the 142 women, and were excluded from the analysis. Of a total of 130 singleton pregnant women, mean TACL and TVCL values were found to be 39.3 ± 6.4 mm and 41.5 ± 7.4 mm, respectively. The mean TACL was found to be shorter than the mean TVCL by an average of 2.2 mm ($p < 0.001$). An intraclass correlation coefficient between both procedures was found to be 0.443 which was statistically significant ($p < 0.001$). Similarly, the difference between TVCL and TACL measurements decreased as BMI increased with statistical significance ($p = 0.043$). The 5th percentile of TACL and TVCL was 31 mm and 32 mm, respectively. None of the patients had a TACL and TVCL < 25 mm which is defined as a short cervix.

Conclusion: The TACL assessment was possible to carry out 91.4% of pregnant women and was moderately correlated with TVCL, therefore, it may be considered as an initial screening tool for cervical length assessment in pregnant women at low-risk for preterm delivery.

Keywords: transabdominal cervical length, transvaginal cervical length, preterm delivery, reliability, measurement.

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ความน่าเชื่อถือของการวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้องเทียบกับการวัดด้วยคลื่นเสียงความถี่สูงทางช่องคลอด ในช่วงอายุครรภ์ 16-24 สัปดาห์

นัตยา บัวทุม, พีระพรรณ พันธุ์ภักดีคุณ, ณัฏฐพล อิ่มสม-สมบูรณ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความน่าเชื่อถือของการวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้องเทียบกับการวัดด้วยคลื่นเสียงความถี่สูงทางช่องคลอด ในช่วงอายุครรภ์ 16-24 สัปดาห์*

วัสดุและวิธีการ: *ทำการศึกษาแบบไปข้างหน้า ในหญิงตั้งครรภ์เดี่ยว ในช่วงอายุครรภ์ 16-24 สัปดาห์ ที่มีข้อบ่งชี้ของการตรวจด้วยคลื่นเสียงความถี่สูง กองสูตินรีเวชกรรม โรงพยาบาลพระมงกุฎเกล้า ระหว่างวันที่ 27 มีนาคม 2560 ถึง 29 ธันวาคม 2560 หญิงตั้งครรภ์ที่เคยผ่าตัดปากมดลูก มีมดลูกหดรัดตัว หรือมีเลือดออกจากช่องคลอด จะถูกคัดออก โดยหญิงตั้งครรภ์ที่เข้าร่วมการศึกษาทั้งหมดจะได้รับการวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้อง หลังจากปัสสาวะทิ้ง และวัดความยาวปากมดลูกทางช่องคลอดตามวิธีที่สมาคมเวชศาสตร์มารดาและทารกในครรภ์ปี 2557 แนะนำ ข้อมูลด้านประชากรศาสตร์และข้อมูลทางการแพทย์ของผู้ป่วยจะถูกบันทึกลงในแบบบันทึกข้อมูล เปรียบเทียบความยาวปากมดลูกที่วัดได้จากทั้งสองวิธี และวิเคราะห์ปัจจัยที่มีผลต่อความแตกต่างของความยาวปากมดลูกที่วัดด้วยคลื่นเสียงความถี่สูงทั้ง 2 วิธี*

ผลการศึกษา: *มีผู้ยินยอมเข้าร่วมงานวิจัยทั้งสิ้น 142 คน มีหญิงตั้งครรภ์ที่ไม่สามารถวัดความยาวปากมดลูกด้วยคลื่นความเสียงถี่สูงทางหน้าท้อง ภายในเวลา 5 นาทีและถูกคัดออกจากการศึกษา 12 คน (ร้อยละ 8.6) หญิงตั้งครรภ์ 130 คนที่ได้รับการวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้องและทางช่องคลอด มีค่าเฉลี่ยของความยาวปากมดลูกที่วัดทางหน้าท้องและทางช่องคลอดคือ 39.3 ± 6.4 และ 41.5 ± 7.4 มิลลิเมตร ตามลำดับ ค่าเฉลี่ยความยาวปากมดลูกที่วัดทางหน้าท้องสั้นกว่าค่าเฉลี่ยความยาวปากมดลูกที่วัดทางช่องคลอด 2.2 มิลลิเมตร ($p < 0.001$) ค่าสหสัมพันธ์ภายในชั้นของการวัดทั้งสองวิธี คือ 0.443 ($p < 0.001$)โดยความแตกต่างระหว่างความยาวปากมดลูกที่วัดทั้ง 2 วิธี จะน้อยลงอย่างมีนัยสำคัญทางสถิติ เมื่อหญิงตั้งครรภ์มีดัชนีมวลกายเพิ่มขึ้น ความยาวปากมดลูกที่วัดทางหน้าท้องและทางช่องคลอด มีค่าเปอร์เซ็นไทล์ที่ 5 เท่ากับ 31 และ 32 มิลลิเมตร ในการศึกษานี้ไม่พบหญิงตั้งครรภ์ที่มีความยาวปากมดลูกสั้น (< 25 มิลลิเมตร)*

สรุป: *การวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้อง สามารถทำสำเร็จในหญิงตั้งครรภ์ร้อยละ 91.4 และค่าที่ได้มีความสัมพันธ์กับค่าที่วัดทางช่องคลอดในระดับปานกลาง จึงอาจพิจารณาให้ตรวจคัดกรองสตรีตั้งครรภ์ที่มีความเสี่ยงต่ำในการคลอดบุตรก่อนกำหนด โดยการวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้อง*

คำสำคัญ: *การวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางหน้าท้อง, การวัดความยาวปากมดลูกด้วยคลื่นเสียงความถี่สูงทางช่องคลอด, การคลอดบุตรก่อนกำหนด, ความเที่ยงของเครื่องมือ*

Introduction

Preterm birth, defined as delivery before a 37 week of gestation[1], is a major determinant of neonatal mortality and morbidity in infants and has long-term adverse consequences for health, especially in very preterm birth infants[2-3]. Preterm birth rates have been reported to account for 12% of all live births[1], and given this prevalence, early detection and management of risk are essential to reduce the occurrence of perinatal morbidity and mortality related to prematurity. There are many methods available for preterm screening, e.g. history taking, usage of home uterine monitors, biochemical marker investigation, and cervical length measurements[4]. Of these methods, several studies suggest that the second trimester cervical length is the best preterm predictor[5-8]. Therefore, preterm reduction strategies in women with mid-trimester short cervixes call for initial screening of second trimester cervical length and further potential progesterone administration[9].

Of the many and varied methods to measure cervical length, the transvaginal sonography (TVS) method is a gold standard for assessing cervical length. The Fetal Medicine Foundation (2014) details protocols for cervical-length measurement, which when performed by trained operators, ensures that results are reproducible with low interobserver variation[10]. Be this as it may, in assessing cervical-length, TVS stands to better identify the 0.12-0.27% of pregnant women with preterm births attributed to short cervixes[11, 12]. Moreover, low-risk women for preterm birth may not receive this assessment due to time constraints or lack of trained operators.

To complicate matters, in a study by Friedman et al.[13], 9.8% of pregnant women declined transvaginal cervical length (TVCL) assessment due to embarrassment, discomfort during the examination, and concerns of safety. In contrast, transabdominal sonography (TAS) is perhaps less inconvenient for woman but has been found to produce less accurate and lower-quality images. This is reported by Marren et al.[14], who found that transabdominal measurement in individuals with full bladders led to overestimates of cervical length by approximately 6.1 mm. However, Peng et al.[15], found that a cervical length evaluated by TAS in individuals with emptied bladders was closely correlated to a cervical length measured transvaginally. This analysis aims to better clarify the reliability of transabdominal cervical length (TACL) measurements in singleton pregnancies at 16-24 weeks of gestation compared with those of transvaginal cervical length (TVCL). In addition, the effect of maternal and pregnancy characteristics on the differences between TACL and TVCL measurements will be considered.

Materials and Methods

This prospective study was conducted in the Obstetrics and Gynecology Department of Phramongkutklao Hospital between 27 March 2017 and 29 December 2017 and received approval from the Institutional Review Board of the Royal Thai Army Medical Department. Participants were asymptomatic singleton pregnant women who underwent ultrasounds between 16 weeks and 24 weeks of gestation with any indications. Women with a history of cervical surgery, uterine contractions, and vaginal bleeding, were excluded. Demographic and medical data were collected through review of electronic medical records.

Cervical length scans were performed by two operators trained in transvaginal and transabdominal ultrasonography using the Aloka Alpha 7. Participants were asked to void and were then placed in a dorsal supine position. The first operator performed a TACL assessment from the external to the internal os in a mid-sagittal plane. Clear identification of the external and internal cervical os was required prior to 3-time assessment, where the shortest linear cervical length was recorded, with fetal scanning occurring thereafter. Upon completing anomaly scans, those with full bladders were asked to void before being placed in a supine position with legs abducted. A second operator, who was blinded to the results of the TACL, performed the TVCL assessment according to the

methods described by the Fetal Medicine Foundation (2014)[11]. If a satisfactory TACL image could not be obtained within 5 minutes, the operator would proceed to the fetal scanning and the TACL was designated as unobtainable.

Cervical length measurements and medically relevant demographic data were analyzed using STATA/MP 12 software. A paired t-test was used to compare the mean of TACL and TVCL values. A Pearson's correlation was then calculated and used to explore the correlation between the procedures, where $p < 0.05$ was considered statistically significant.

Sample size calculations are based on Peng et al.[15] which reported the mean TACL and TVCL to be 36.0 ± 4.9 mm and 37.6 ± 5.4 mm, respectively. Sample size was calculated via the one population mean formula, where in order to obtain a statistical power of 90% and a p-value of 0.05, a population size of approximately 110 participants was required.

Results

One hundred and forty-two women with singleton pregnancies who met the inclusion criteria agreed to participate in the study. Satisfactory TACL images could not be obtained within 5 minutes in 12 (8.6%) cases, and were thusly excluded from the analysis. As a result, 130 TVCL and TACL measurements were obtained, of which demographic information can be found in Table 1.

Table 1. Demographic data (N = 130).

Demographic data	n (%)
Gravid	
Nulliparous	72 (55.4)
Multiparous	58 (44.6)
Gestational age, Mean (SD)	19.6 (2.4)
Pre-pregnancy BMI, Mean (SD)	22.3 (4.4)
Underweight, <18.5 kg/m^2	17 (13.1)
Normal, 18.5-22.99 kg/m^2	72 (55.4)
Overweight, 23-24.99 kg/m^2	13 (10)
Obese, 25-29.99 kg/m^2	21 (16.1)
Morbidly obese, 30 kg/m^2	7 (5.4)

BMI: body mass index

Among 130 women, both the external and internal os were clearly identified in all women using the TVS approach. The mean TACL and TVCL values were 39.3 and 41.5 mm, respectively (Table 2). Additionally, the 5th percentile of TACL and TVCL were 31 mm and 32 mm, respectively. Importantly, none of the participants of this study were found to have short cervixes (TVCL < 25 mm).

Fig. 1. provides a graphical representation of the correlation between TACL and TVCL. The intraclass correlation coefficient between both procedures was 0.443 which was statistically significant ($p < 0.001$) and plottable via the following equation: TA cervical length (mm) = 0.384 * TV cervical length (mm) + 23.38 mm.

As per the regression equation, a length of 25 mm in the TVCL approach corresponded to 32.98 mm in length in the TACL approach. The below

Blande-Altman plot further represents paired differences between TACL and TVCL groups (Fig. 2), where the mean TACL was shorter than the mean TVCL by an average length of 2.2 mm ($p < 0.001$).

This study also found that the difference between TVCL and TACL values decreased as BMI increased with statistical significance (Pearson's coefficient = - 0.178, $p = 0.043$) (Fig. 3).

The distribution of TACL and TVCL values, as seen in Fig. 4, indicates that none of the participants were found to have short cervixes, i.e. cervical length of less than 25 mm.

Table 2. Summary of TACL and TVCL measurements (mm).

	TACL (mm)	TVCL (mm)
N	130	130
Mean	39.3	41.5
SD.	6.4	7.4
Minimum	25	25.9
Maximum	62	76
Percentile:		
5th	31	32
10th	32	33.5
50th	39	41
90th	49	49
95th	51.2	54

TACL: transabdominal cervical length, TVCL: transvaginal cervical length

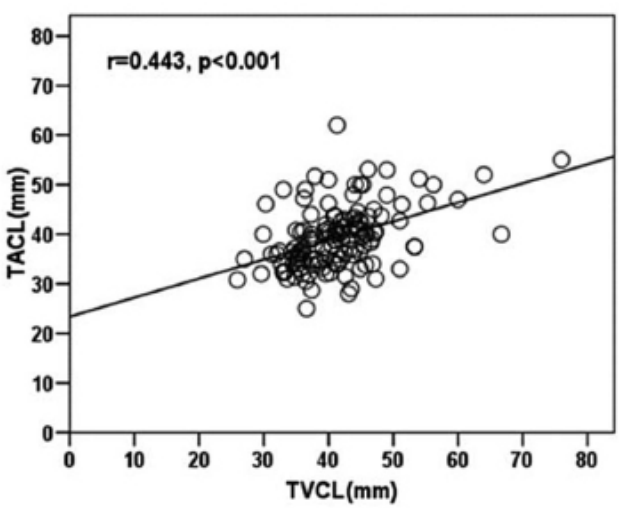

Fig. 1. Relationship between TVCL and TACL (TACL: transabdominal cervical length, TVCL: transvaginal cervical length)

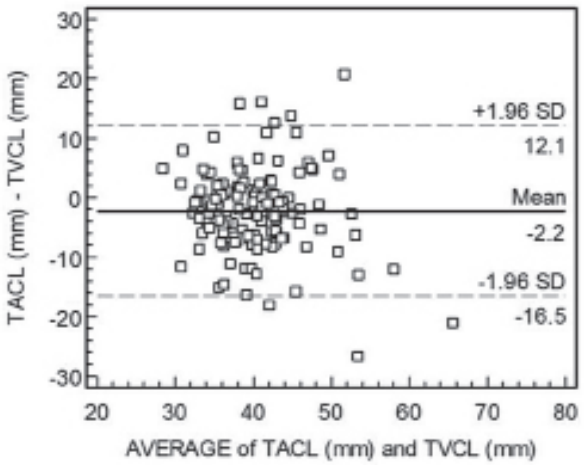

Fig. 2. Paired differences between TACL and TVCL (TACL: transabdominal cervical length, TVCL: transvaginal cervical length)

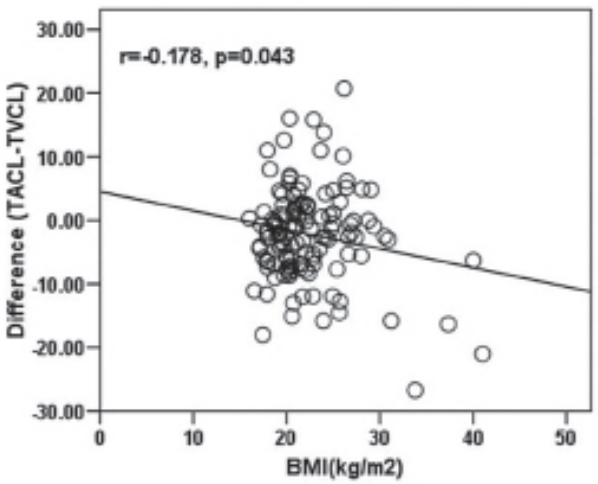

Fig. 3. Correlation between differences in cervical length and body mass index (BMI) (TACL: transabdominal cervical length, TVCL: transvaginal cervical length)

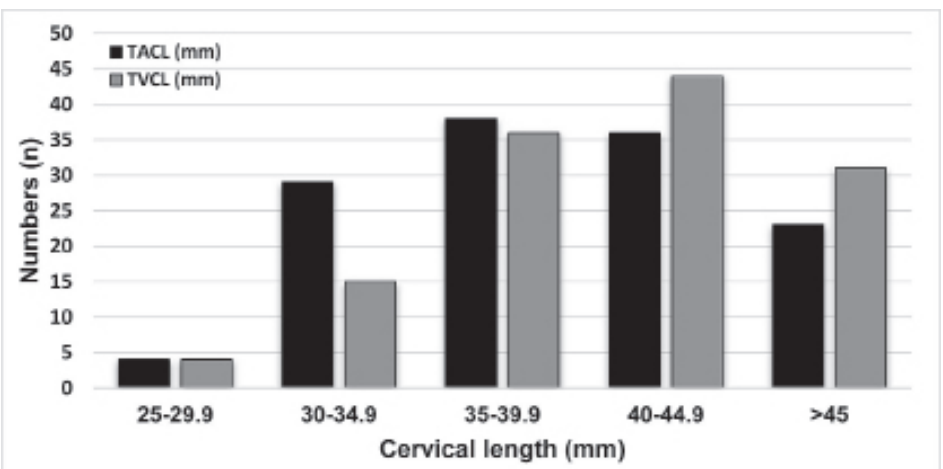

Fig. 4. Distribution of TVCL and TACL (TACL: transabdominal cervical length, TVCL: transvaginal cervical length)

Discussion

The risk of spontaneous preterm delivery increases as cervical length decreases[16] and TVCL assessment is an effective method for identifying women at risk of preterm delivery[16, 17]. Despite this, in a study by Romero et al.[18] it was found that short cervixes are present in approximately 1.7% of low-risk populations. Given this low prevalence, routine transvaginal ultrasound screenings in pregnant women may not be the most cost-effective and efficient method to identify the 1.7% of patients who have short cervixes, especially in crowded and busy obstetric units in public hospitals. As satisfactory TACL images were obtained within a few minutes in 91.4% of subjects, preforming a TACL assessment at the time of the routine 2nd trimester ultrasonography would not greatly increase total examination times. This analysis found a fair correlation between obtained TACL and TVCL measurements when performed by trained operators. Hence, TACL measurements may be utilized as an initial tool for cervical length assessment in low-risk populations. If unsuccessful, it is recommended that TVCL be conducted.

As stated, this study found a moderate correlation between TVCL and TACL measurements ($r = 0.443$, $p < 0.001$) which was similar to values found in Hernandez-Andrade et al.[19] ($r = 0.49$; 95% CI = 0.39-0.56). Conversely, Saul et al.[20] and Peng et al.[15] reported a strong correlation between TACL and TVCL measurements ($r = 0.824$ and 0.808, respectively), which was much higher than values obtained in this study. In the case of Saul et al. this difference may be the result of TACL and TVCL inspections being performed by the same sonographer, while differences with those of Peng et al.[15] may be due to differing gestational ages at the time of assessment.

In research concerning TVCL and TACL, a common trend of contradictory data comprising over- and underestimations between both metrics adopted in this study, can be found. Hernandez-Andrade et al.[19] reported that assessment via TAS underestimated cervical length by an average of 1.1 mm in pregnant women with cervical length ≥ 25 mm. These findings are in line with many works of research which found that TACL-values were shorter than the TVCL by a mean value of 1.6, 2.6, and 4.8 mm, respectively[21, 22, 15]. Peng et al.[15] reported that in the cases of short cervixes (< 25 mm), transabdominal scanning could elicit either underestimated or overestimated cervical lengths. In this study, the TACL was shorter than the TVCL by an average of 2.2 mm. Although none of the subjects of this study were found to have short cervixes, the aforementioned finding was similar to those found in other studies which considered shorter cervixes among the TACL group[13, 21].

With regards to the correlation of differences in cervical length and BMI, this analysis found that as BMI increased, cervical length differences decreased with statistical significance. This contradicts previous studies by Peng et al. (15), which found that the difference between TVCL and TACL tended to increase as BMI increased but with no statistical significance. To clarify this, further large-scale studies should be conducted which consider populations of short cervix and obese groups thus better elucidating the relationship between these variables.

Saul et al.[20] proposed a TACL cut-off value of 30 mm to more clearly identify pregnant woman with a short cervix. Stone et al.[21] suggested a TACL < 27 mm as an indication to perform TVCL; whereas, Peng et al.[15] proposed the 5th percentile of TACL (29 mm) as a threshold to perform TVCL. This analysis lacked subjects with cervix lengths < 25 mm, and therefore could not propose such threshold values.

The maternal bladder filling status has a major impact on TACL measurements[14]. Urine has been purported to facilitate clear visualization of the cervix and the margin of internal and external os via TAS[5]. Yet, a full bladder confounds assessments, producing overestimations of cervical length by approximately 6.1 mm[14] as well as producing feelings of discomfort for the subjects. Conversely, TACL measurements in subjects with emptied bladders have been reported to show good correlation with TVCL in prior studies[13]. This analysis found a high success rate of TACL obtainment (91.4%) after voiding. This may be due to

improvements in ultrasound imaging resolution when compared with previous studies.

This study was limited in several areas comprising the following initial points of consideration. Firstly, no patients with short cervixes (TVCL < 25 mm) were identified in all 130 participants. This may have been the result of a lower prevalence of a short cervix in Thai populations[23]. Because of this, it was not possible to determine the efficacy of TAS in diagnosing short cervixes and, subsequently, to investigate the correlation of TACL and TVCL in pregnant women with short cervixes. Additionally, characteristics of pregnant women with unsuccessful transabdominal cervical length measurement were not analyzed, yet such data may be useful in identifying medically important factors of pregnant women who are well-suited for TACL assessment.

Although universal cervical length screening remains controversial, doing so to identify women at risk of preterm birth is of great benefit, as progestin and cervical cerclage can reduce risk of preterm birth due to short cervixes in pregnant women[11, 12]. This study found that satisfactory cervical images were obtainable via TAS in 91.4% of pregnant women. Furthermore, a moderate correlation between TVCL and TACL measurements was found ($r = 0.443$, $p < 0.001$). Therefore, TACL may be considered a potential initial tool for screening low-risk pregnant women, and this may be an important instrument in reducing obstacles to universal cervical length screening in crowded and busy obstetrics units.

Conclusion

TACL was assessable in 91.4% of pregnant women and was moderately correlated with TVCL, therefore, it may be an initial screening tool for cervical length assessment in populations at low-risk for preterm birth.

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Potential conflicts of interest

The authors declare no conflict of interest.

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