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TJOG is the official journal of RTCOG. This is a double-blind peer-reviewed journal aiming to promote academic knowledge and provide a forum for publication in Obstetrics and Gynecology. First issue of TJOG (Volume 1) was published in June 1989.

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

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Reviewer acknowledgement 2019

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EDITORIAL

This fourth issue of Thai Journal of Obstetrics and Gynaecology (TJOG) contains many interesting articles. The special article in this issue is "**Adjuvant Chemotherapy for Malignant Ovarian Germ Cell Tumors in Pregnancy**"

We are pleased to announce that TJOG has been accepted for inclusion in the SCOPUS database. The journal editorial team would like to thank the TCI-TRF-SCOPUS Collaboration Project, Thai-Journal Citation Index (TCI) Center, and the local board for their constructive feedback contributing to the journal quality improvement. Future articles to be published in our journal will be indexed in **SCOPUS**, as well as **TCI** and **ACI** (ASEAN Citation Index). We thank to all the authors, readers, reviewers, and editors for your contributions to TJOG.

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.

Editor in Chief and managing staff already attended "**Web of Science Group Editor Day 2019 - Journal Selection Process**" on Wednesday 28 August 2019 at Convention Hall C & D, Level 1, Ambassador Hotel Bangkok, 171 Sukhumvit Soi 11, Bangkok, Thailand.

Editorial Board of TJOG look forward to continuously raising the quality of the TJOG and prepare journal for submission to be evaluation for the 4th round re-evaluation for TCI indexed journals (2020-2024).

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

Thai Journal of Obstetrics and Gynaecology
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SPECIAL ARTICLE

Adjuvant Chemotherapy for Malignant Ovarian Germ Cell Tumors in Pregnancy

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ABSTRACT

Malignant ovarian germ cell tumors (MOGCTs) are uncommon in pregnancy, and therefore few gynecologic oncologists obtain expertise in this area. Management of MOGCTs in pregnancy is complicated and complex, requiring a multidisciplinary team in a specialized center. Fertility-sparing surgery is the first choice treatment of MOGCTs, while adjuvant chemotherapy is reserved for high risk cases. The indications for adjuvant chemotherapy after surgery are similar to those for non-pregnant women. Due to the low incidence and insufficient published data, the decision concerning adjuvant chemotherapy is based on case reports or small retrospective cohort studies. Following is a brief review of current knowledge concerning the MOGCTs in pregnancy and its management, especially, adjuvant chemotherapy.

Keywords: malignant ovarian germ cell tumor, ovarian cancer, pregnancy, management, chemotherapy.

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Introduction

Malignant ovarian germ cell tumors (MOGCTs) are infrequent form of ovarian tumors, arising from germ cells of the embryonic gonad. These tumors often grow rapidly, causing acute abdominopelvic pain that lead to early detection and treatment, thus these tumors are most often diagnosed in their early stages. They also usually occur in young women and are often unilateral. Nowadays, fertility-sparing surgery is the cornerstone primary treatment for MOGCTs, while adjuvant chemotherapy is kept for selected or high risk cases (generally indicated in all cases except for stage IA dysgerminoma or grade 1 immature teratoma)[1].

The incidence of MOGCTs in pregnancy is estimated at 1 in 12,500-25,000 pregnancies[2].

With the increasing use of routine ultrasonographic screening in pregnant women, it is forecast that more pregnant women will be diagnosed with ovarian cancer, especially MOGCTs, in the future.

When management of MOGCTs in pregnancy is considered, the gynecologic oncologist needs to carefully balance fetal (fetal loss, treatment-related complications to the fetus), maternal (potential loss of the reproductive function after cancer treatment, anxiety) and malignancy (oncological outcomes) concerns[3]. The management of MOGCTs in pregnancy, especially the decision whether or not to include adjuvant chemotherapy, is complicated. Due to insufficient data and the lack of randomized clinical studies, the decisions concerning adjuvant chemotherapy are based on a small number of case reports or small retrospective cohort studies[4]. Herein following is a short survey of current knowledge on adjuvant chemotherapy for MOGCTs in pregnancy (including data on safety outcomes for mother and fetus).

Clinical / pathological profiles

In a systematic review covering 102 MOGCTs in pregnancy, the two most common histological types were dysgerminoma and endodermal sinus tumor (EST)[3]. The median age of these women was 25.8 years, and 35.3% had abdominal/pelvic pain, 19.6% had abdominal distension, and 19% had growing mass. Accidental tumor discovery, such as during routine ultrasound, was reported in 21.6% of the cases[3].

Treatment during pregnancy

Fertility-sparing surgery with full peritoneal staging (peritoneal biopsy, omentectomy or omental biopsy, and peritoneal washing) should be done, but routine pelvic and para-aortic lymphadenectomy during surgery are not indicated[5, 6], although suspicious palpable lymph nodes should be removed. The indications for adjuvant chemotherapy after surgery are similar to those in non-pregnant women[6, 7].

Adjuvant Chemotherapy

Maternal physiological changes and stage of fetal development (the all-or-none period, organogenesis, and fetal phase) are the two most important factors when considering chemotherapy in pregnant women[8-10].

Several physiologic changes during pregnancy such as alterations in blood volume, albumin levels, hepatic metabolism and renal elimination may affect the pharmacokinetics of chemotherapeutic drugs, and consequently it is difficult to decide the optimal dose of chemotherapy that will actually be transported to the tumor site, perhaps leading to reduced drug effectiveness[9-11]. However, there is no evidence at present that dose adjustments are necessary to improve efficacy[10], and the current guideline recommends dosing chemotherapeutic drugs in pregnancy according to the women's weight[9].

The first trimester is the period of organogenesis of the fetus, and chemotherapy is contraindicated during this trimester to avoid interference with organogenesis, as early chemotherapy treatment has been correlated with a 10% to 20% risk of malformation[8, 9, 12, 13]. The risk of malformation drops to 1.3% in the third trimester[13]. From several previous studies and reviews, it appears that administration of some chemotherapeutic agents (such as bleomycin, platinum agents, anthracyclines, and taxanes) after the first trimester is relatively safe. However, there are also relatively higher risks of premature rupture of membranes, preterm labor, low birth weight, intrauterine growth restriction, and still birth[3, 8, 9, 11, 13-15]. Thus, in general the fetal benefits of delaying chemotherapy treatment until the second trimester counterbalance the increased maternal risks[9].

Chemotherapy should be avoided after 35 weeks of gestation or stopped 3 weeks before the expected date of delivery to allow recovery from possible bone marrow suppression of both mother and newborn, and to reduce the maternal risk of bleeding and infection[8-10].

Chemotherapy drugs and combination regimens

In pregnant women with MOGCTs, the indications for adjuvant chemotherapy after surgery are mostly similar to those in non-pregnant women with MOGCTs[4, 7]. From the 1990s until now, the combination of bleomycin, etoposide and cisplatin (BEP) has been considered the first line or standard regimen for adjuvant chemotherapy for non-pregnant women with MOGCTs[1]. For MOGCTs during pregnancy. There are conflicting datas in using BEP as a first line standard of treatment[7].

In 1999, Elit et al. reported a case of neonatal complications after BEP treatment of an EST during pregnancy. The neonate was born with significant ventriculomegaly with cerebral atrophy after 1 cycle of BEP during the third trimester[16]. In another case, a neonate suffered hearing impairment after being exposed to BEP treatment in utero[4, 17]. Based on this poor neonatal outcome and given the paclitaxel activity in MOGCTs[4,18], paclitaxel and carboplatin (PC) is becoming a point of interest[15]. In 2007, Hubalek et al., reported the first case of dygerminoma in a pregnant woman treated with PC during the third trimester with good response, and no adverse effects on the fetus[15]. Vinca alkaloids (especially vinblastin) has been in use for a long period of time, and the oncological outcome of patients with stage I MOGCTs treated with bleomycin, vinblastin and cisplatin (BVP) is nearly similar to that of those treated with BEP[3, 4, 19]. In addition, many case reports have found their use relatively safe in pregnancy[3, 4, 20, 21]. Based on the possible fetal risk and the high risk of secondary leukemia after etoposide treatment, two international consensus meetings (3rd of July 2008 and 17th of May 2013, both in Leuven, Belgium) suggested that PC or BVP should be considered in pregnant women with MOGCTs[4, 22].

Also, since 2000, several studies, including a systematic review of the literature, have reported that etoposide use during pregnancy (after the first trimester) in combination with cisplatin with or without bleomycin appeared to be safe[3, 23-26]. Consequently, in 2019, a third international consensus meeting suggested that BEP or etoposide with cisplatin (EP) should be preferred as adjuvant chemotherapy for pregnant women with MOGCTs[9].

Conclusion

MOGCTs during pregnancy are rare. Management of this cancer is an especially difficult issue as both the mother and fetus may be influenced. Unfortunately, decision concerning the optimal therapeutic management including adjuvant chemotherapy for this cancer is mainly based on case reports and small retrospective studies. In addition, data regarding long term outcomes of individuals exposed to adjuvant chemotherapy during pregnancy are limited. Thus, therapeutic decisions and treatment should be undertaken in specialized centers, and with personalized counselling.

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GYNECOLOGY

Comparison of Lidocaine Spray in Conjunction with Intrauterine Lidocaine versus Paracervical Block for Pain Relief in Fractional and Curettage: A randomized controlled trial

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ABSTRACT

Objectives: To compare lidocaine spray plus intrauterine lidocaine versus paracervical block alone for pain relief during and at 30 minutes after fractional curettage.

Materials and Methods: One hundred and twelve women with abnormal uterine bleeding at Khon Kaen Hospital from January to April, 2018 were randomly allocated into two groups, receiving lidocaine spray in conjunction with intrauterine lidocaine (n = 56) versus paracervical block (n = 56) before fractional curettage. Pain score during fractional curettage was measured by 100-mm visual analogue scale (VAS). Pain score after procedure and all adverse events were observed and recorded at 30 minutes after procedure by other doctors who did not perform fractional curettage. Moreover, additional analgesia or sedation, and inadequacy of specimen were also recorded.

Results: Baseline characteristics were similar between groups. Median pain score during procedure in lidocaine spray in conjunction with intrauterine lidocaine group was significantly lower than paracervical block group (50.5 (39-63), 95% vs 71.5 (53.5-82.5) Confidence interval 12.70-28.25, $p < 0.001$). There were no significant differences in pain score after procedure, adverse events, additional analgesia or sedation and inadequacy of specimen.

Conclusion: Lidocaine spray in conjunction with intrauterine lidocaine had significant difference for pain reduction when compared with paracervical block during fractional curettage without serious adverse events.

Keywords: fractional curettage, lidocaine spray, intrauterine lidocaine, paracervical block, pain score, visual analog scale

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ผลของการพ่นยาชาที่ปากมดลูกร่วมกับการฉีดยาชาเข้าโพรงมดลูกเปรียบเทียบกับการฉีดยาชาข้างปากมดลูกเพื่อลดความปวดในการขูดมดลูกแบบแยกส่วน:การทดลองแบบสุ่ม

ภิญญา เอื้อพงศ์การุณ, ชินวัฒน์ ศรีนิล, มาลีชาติ ศรีพิพัฒนะกุล, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาการใช้ยาชาชนิดพ่นร่วมกับการฉีดยาชาเข้าโพรงมดลูก เปรียบเทียบกับการฉีดยาชาข้างปากมดลูก ในการลดความปวดระหว่างการขูดมดลูกแบบแยกส่วน และหลังจากขูดมดลูก 30 นาที*

วัสดุและวิธีการศึกษา: *สตรีที่มีภาวะเลือดออกผิดปกติทางช่องคลอดและมีข้อบ่งชี้ในการขูดมดลูกที่เข้ารับการรักษาระหว่างเดือนมกราคมถึงเดือนเมษายน ปี 2561 จำนวน 112 คน ถูกสุ่มแบ่งเป็นสองกลุ่มเพื่อรับการพ่นยาชาที่ปากมดลูกร่วมกับฉีดยาชาเข้าโพรงมดลูก เปรียบเทียบกับการฉีดยาชาข้างปากมดลูก โดยประเมินความเจ็บปวดขณะและหลังขูดมดลูก 30 นาทีโดยแพทย์ที่ไม่ได้ทำการขูดมดลูก รวมทั้งประเมินภาวะแทรกซ้อนจากการใช้ยา ความต้องการยาแก้ปวดชนิดอื่นๆเพิ่มเติม และความสามารถในการอ่านผลชิ้นเนื้อ ตัววัดที่สำคัญคือคะแนนความเจ็บปวดในขณะและหลังขูดมดลูก 30 นาที*

ผลการวิจัย: *ลักษณะทางประชากรศาสตร์ไม่แตกต่างกันระหว่างกลุ่ม ระดับความปวดในกลุ่มที่ได้รับการพ่นยาชาที่ปากมดลูกร่วมกับฉีดยาชาเข้าโพรงมดลูกน้อยกว่ากลุ่มที่ได้รับการฉีดยาชาข้างปากมดลูกซึ่งแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่ามัธยฐานของกลุ่มควบคุม 50.5 คะแนน (39-63), กลุ่มทดลอง 71.5 คะแนน (53.5-82.5), p<0.001) และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระดับความปวดหลังขูดมดลูก 30 นาที ภาวะแทรกซ้อนรุนแรง ความต้องการยาแก้ปวดชนิดอื่น และชิ้นเนื้อที่ไม่สามารถแปลผลได้ในงานวิจัยนี้*

สรุป: *การพ่นยาชาที่ปากมดลูกร่วมกับฉีดยาชาเข้าโพรงมดลูก สามารถลดความปวดขณะขูดมดลูกได้อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับการฉีดยาชาข้างปากมดลูก และไม่พบภาวะแทรกซ้อนที่อันตราย*

คำสำคัญ: *การขูดมดลูกแบบแยกส่วน, การฉีดยาชาเข้าโพรงมดลูก, การฉีดยาชาข้างปากมดลูก, การพ่นยาชาที่ปากมดลูก, การให้คะแนนความปวดโดยใช้มาตรวัดด้วยสายตา*

Introduction

Fractional curettage is a common procedure for investigating causes of abnormal uterine bleeding. Patients frequently experience moderate to severe pain during this procedure. Many studies showed pain scores with cervical biopsy and cervical curettage ranging from 4-6 and endometrial biopsy ranging from 5-7 on visual analogue scale (VAS)[1].

General anesthesia is recommended by the Royal Thai College of Obstetricians and Gynecologists (RTCOG) for pain reduction during fractional curettage. It provides amnesia and hypnotic effect and associated with increased mortality and morbidity[2].

Paracervical block is effective for pain reduction by relieving pain in the lower part of uterus and cervix through the uterovaginal plexus and was recommended by RTCOG 2013 in fractional curettage guideline. However, it does not provide completely pain relief and need to use adjunctive medications including intravenous sedative drugs, oral nonsteroidal anti-inflammatory drugs (NSAIDs) or anxiolytic drugs. Moreover, it can be associated with adverse events such as numbness around month, dizziness to convulsion and respiratory arrest[3].

Systematic review[4] showed that there was no evidence that paracervical block reduced pain when compared to alternative regional anesthetic methods or systemic analgesics and sedatives.

Lidocaine spray can be used for pain relief during gynecologic operations. This drug is simple and convenient to use. It acts by reduction of peripheral pain impulses or damaged nociceptors below the application site[5]. Therefore, it can reduce pain during tenaculum placement and during endocervical curettage. However, the adverse effects of lidocaine spray remains unclear.

Intrauterine lidocaine acts by blocking nerve endings in the uterine corpus and fundus. It is logical to add intrauterine lidocaine to lidocaine spray to enhance anesthetic effect.

However, it remains controversial about pain relieving effect in gynecologic procedures and there is still no consensus that which type of analgesia should be used in patients undergoing fractional curettage. Thus, the objective of this study was to compare lidocaine spray in conjunction with intrauterine lidocaine versus paracervical block for pain reduction during fractional curettage.

Materials and Methods

This randomized controlled trial was conducted at Khon Kaen Hospital, Thailand from January to April, 2018. This study was approved by Khon Kaen Hospital Institute Review Board in Human Research. All participants were informed about the study and signed the consent form before enrollment.

We included women with abnormal uterine bleeding age 35 years old or more who were scheduled for fractional curettage. Women with severe genital organ infection, cervical stenosis, history of lidocaine hypersensitivity, impaired liver function, coagulopathy or women who took anticoagulant or antiplatelet drugs, pregnant women and those who were unable to understand how to score VAS were excluded.

Eligible participants were randomized by computer generated with block of four and randomly assigned into two groups; lidocaine spray in conjunction with intrauterine lidocaine and paracervical block. The random numbers were put in the sequentially sealed, opaque envelopes.

The study group received two puffs of lidocaine spray administered on cervical surface and wait for three minutes to allow the anesthetic to take effect, then tenaculum was placed. Afterwards, intrauterine lidocaine was performed by using 5 ml of 2% lidocaine with 1:100,000 epinephrine administered into the uterine cavity through a 2-inch, 16-gauge venous catheter inserted through the cervical canal and was left for 3 minutes to prevent back flow and to allow contact time to take effect. After that, endocervical and endometrial curettage were performed, respectively.

The control group received paracervical block performed by using 23-gauge spinal needle injected at 3 and 9 o'clock of cervicovaginal reflection at depth of 1 cm then push 5 ml of 2% lidocaine with epinephrine 1:100,000 into each side and wait for 5 minutes. Then,

endocervical and endometrial curettage were performed, respectively.

The fractional curettage was performed by using tenaculum grasped the anterior lip of the cervix and endocervical curettage was performed by using a curette number 00, after that we used uterine sound to measure uterine depth and then uterine curettage was performed by curette number 0. Women were observed for two to four hours at gynecology ward by nurses. Vital signs were recorded immediately when lidocaine spray, intrauterine lidocaine, paracervical block, endocervical curettage and endometrial curettage was performed, and also monitored at 30 minutes, 2 and 4 hours after procedure. All adverse events were observed and recorded at 30 minutes after procedure. We made an appointment at 14 days after procedure to inform pathological report.

The primary outcome was pain score during endometrial curettage (15 seconds after inserting curette number 0 and endometrial curettage was performed for the first time) which was first pain perception and other doctors asked patients to mark VAS pain score immediately for reducing recall bias. The secondary outcomes were pain score at 30 minutes after procedure, adverse events, additional analgesia or sedation and inadequacy of specimen.

The sample size was calculated from pilot study. We used formula for test of difference in two independence means with alpha of 0.05, power of 90% and 10% dropouts. The sample size was 56 cases per group.

$$n/\,group = \frac{2(Z_{\alpha/2} + Z_{\beta})^{2}\delta^{2}}{(\mu_1 - \mu_2)^2}$$

Statistical analysis was performed using SPSS 17.0 software. Categorical variables were analyzed by Chi-square test or Fisher's extract test. Continuous variables were analyzed by student t-test and Mann-Whitney U-test depended on data distribution. The primary outcome was presented as median with interquartile range with 95% confidence interval. Other outcomes were presents as percentage and median with interquartile range (IQR). P value less than 0.05 was represented statistical significance.

Results

One hundred and twelve women with abnormal uterine bleeding at Khon Kaen Hospital from January to April, 2018 were randomly allocated into two groups, group 1 received lidocaine spray in conjunction with intrauterine lidocaine (n = 56) and group 2 received paracervical block (n = 56) before performed fractional curettage. There was no dropout in this study. Subjective pain experience was measured by100-mm VAS (Fig. 1).

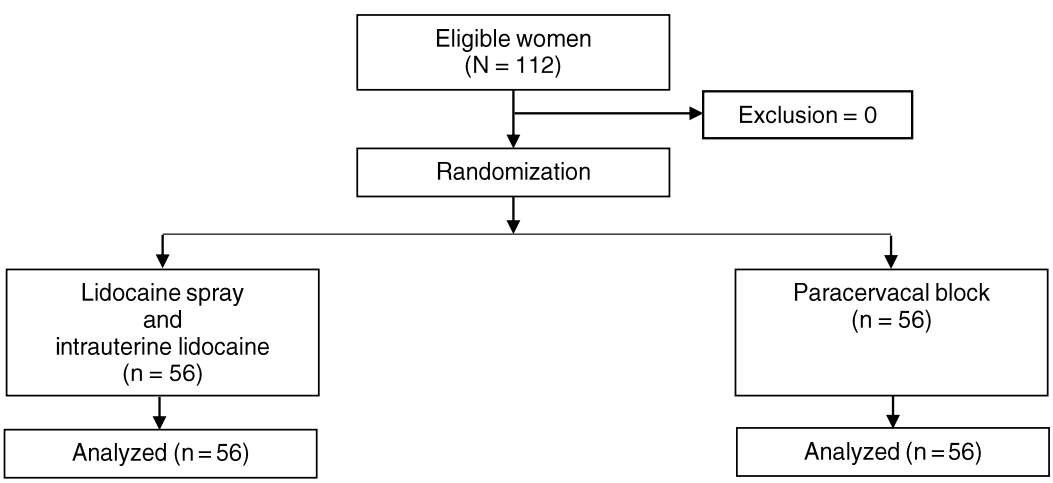

Fig. 1. Study flow diagram.

Baseline characteristics including age, body mass index (BMI), parity, prior curettage, menopausal status and indication for fractional curettage were similar between groups (Table 1). Median pain score (IQR) in lidocaine spray in conjunction with intrauterine lidocaine was significantly lower than paracervical block (50.5 (39-63), 95% CI 12.70-28.25 vs. 71.5 (53.5-82.5), 95% CI 12.70-28.25, p<0.001). Pain score 30 minutes after procedure which was lower in study group but no statistical significance between two groups (Table 2). None of the patients requested termination of fractional curettage or rescue medication. Adverse events found in both groups but without significant difference (lightheadedness, palpitation, numbness of lips, tinnitus and hypotensive event). There was also no difference in inadequacy of specimen (Table 3).

Table 1. Baseline characteristics.

Characteristics	Lidocaine spray and intrauterine lidocaine (n = 56)	Paracervical block (n = 56)	p value
Age (years), median (IQR)	46.50 (40-50)	46 (43-50)	0.606
BMI (kg/m2), mean (SD)	26.65 (4.81)	25.29 (4.15)	0.178
Multipara, n (%)	44 (78.57)	49 (87.50)	0.157
Prior curettage, n (%)	3 (5.36)	9 (16.07)	0.062
Post menopausal status, n (%)	7 (12.50)	7 (12.50)	1.000
Indication, n (%)			0.733
- Abnormal uterine bleeding	46 (82.14)	46 (82.14)	
- Post menopausal bleeding	8 (14.29)	6 (10.71)	
- Endometrial hyperplasia	1 (1.79)	3 (5.36)	
- Tamoxifen used	0	0	
- Other	1 (1.79)	1 (1.79)	

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

Table 2. Primary and secondary outcomes.

VAS pain score	Lidocaine spray and intrauterine lidocaine (n = 56)	Paracervical block (n = 56)	p value	95% CI
During procedure, median (IQR)	50.50 (39-63)	71.50 (53.50-82.50)	< 0.001	12.70-28.25
After procedure, median (IQR)	11.50 (1.50-27.50)	20 (0.50-37.50)	0.190	-2.14-12.78

VAS: visual analogue scale, CI: confidence interval, IQR: interquartile range

Table 3. Adverse events, additional analgesia and inadequacy of specimen.

	Lidocaine spray and intrauterine lidocaine (n = 56)	Paracervical block (n = 56)	p value
Adverse events, n (%)			
- Lightheadedness	2 (3.57)	3 (5.36)	0.647
- Palpitation	1 (1.79)	1 (1.79)	1.000
- Numbness of lips	0	0	
- Tinnitus	2 (3.57)	0	0.154
- Hypotensive event	4 (7.14)	5 (8.93)	0.121
Additional analgesia, n (%)	0	0	NA
Inadequacy of specimen, n (%)	8 (14.29)	5 (8.93)	0.783

Discussion

The present study demonstrated that lidocaine spray in conjunction with intrauterine lidocaine had significantly lower pain score than paracervical block during performing endometrial curettage. The combinations of lidocaine spray and intrauterine lidocaine have synergistic effects on both uterus and cervix. Pelvic splanchnics nerves (S2-4) or known as Frankenhauser plexus innervate lower part of uterus and cervix which is blocked by paracervical block. However, uterus also receives nerve supply from sympathetic nerves (T10-L1) or hypogastric nerves which innervate uterine fundus and body blocking by intrauterine lidocaine. Moreover it can reduce other pain perception by blocking nerve plexus on endometrium[11,12], whereas mucosal surface of cervix also receives innervation by ascending and descending roots which is the limitation of paracervical block to block these nerves but intrauterine lidocaine has this action. Therefore, addition of lidocaine spray has effect to damage nociceptors on cervix and endocervix by reducing peripheral pain impulses[5].

From previous studies and systematic review[4] showed that no evidence of paracervical block alone can reduce pain when compared to alternative regional anesthetic methods or systemic analgesics and sedatives. By the way, there was no study comparing lidocaine spray in conjunction with intrauterine lidocaine versus paracervical block as this study.

Aashima et al[7] conducted randomized controlled trial in 84 patients with abnormal uterine bleeding undergoing fractional curettage. All patients received NSAIDs and paracervical block in conjunction with either 5 ml of 2% intrauterine lignocaine or saline. They figured out statistically significant difference in the pain score between two groups (5.36±1.2 versus 6.81±1.4, $p < 0.001$). In addition, a randomized controlled trial study in 230 patients by Leelawattanakul et al[8] found that intrauterine lidocaine and paracervical block statistically reduce pain during fractional curettage when compared with paracervical block alone (45 (3-61) versus 53 (35-82), $p = 0.002$).

Gökhan et al[9] conducted a randomized controlled trial in 144 patients undergoing fractional and curettage. They compared 2 puffs of lidocaine spray, 25 mg of oral dexketoprofen trometamol, 100 mg of subcutaneous pethidine, 1,000 mg of intravenous paracetamol and 75 mg of oral diclofenac versus placebo and found that every interventions reduced pain perception with statistical significance (4 (2-6) versus 5.5 (4-8) versus 5 (4-5.5) versus 6 (5-8) versus 5 (5-7.5) versus 9 (7-10), p value < 0.001), respectively, but without statistical significance between intervention groups. However, there was a limitation about sample

size among intervention groups which was too small.

Another problem of using anesthetic agents is their adverse effects which range from mild toxicity such as numbness of lips, tinnitus and dizziness to severe toxicity such as convulsion and respiratory arrest. Therefore, some studies monitored lidocaine toxicity by evaluating plasma lidocaine level[13]. In our institute, we could not provide plasma lidocaine level, therefore, we observed clinical of lidocaine toxicity such as numbness of lips, lightheadedness, tinnitus, hypotensive event and convulsion. Adverse events from lidocaine that found in this study such as lightheadedness, palpitation, tinnitus and hypotensive event were not statistically different.

In addition, we concerned about adequacy of specimen because of using intrauterine lidocaine which was infiltrated into uterine cavity might have an affect on obtaining endometrium but there was no statistically significant between two groups.

The strengths of this study were no patients who loss to follow-up and the interventions were easy to perform but we cannot blind doctors and nurses who performed procedure which was the weakness of this study.

Conclusion

Lidocaine spray in conjunction with intrauterine lidocaine had better pain relief during fractional curettage than paracervical block without serious adverse events.

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Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Prevalence and Associated Factors of Positive Margins of Cervical Tissue from Loop Electrosurgical Excision Procedure

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ABSTRACT

Objectives: The primary objective was to find the prevalence of positive margins of cervical tissue from loop electrosurgical excision procedure (LEEP) for conization and the secondary objective was to determine its associated factors.

Materials and Methods: Medical records of 350 patients who underwent LEEP at Udonthani Hospital form March 2016 to July 2018 were reviewed. Data collection included baseline characteristics, preoperative cytology, colposcopic finding, colposcopic directed biopsy histology, histopathological diagnosis, margin of surgical specimens and all related histologic results. The prevalence and associated factors for positive margins were analyzed.

Results: There were 323 patients who underwent LEEP and had complete data. The mean age was 42.3 ± 10.6 years. The majority of them had a body mass index < 30 kg/m2 (94.1%), multiparous (88.8%), negative test of human immunodeficiency virus antibody (91.3%) and premenopausal status (76.2%). The prevalence of positive margins of cervical tissue form LEEP was found in 80 cases (24.8%), and the most positive margin site was endocervix (48.8%). From multivariate logistic regression analysis, colposcopic directed biopsy histology > cervical intraepithelial neoplasia 2 was the only significant factor associated with the positive margins (adjusted odds ratio 3.91, 95% confidence interval 1.35-11.27).

Conclusion: The prevalence of positive margins of cervical tissue from LEEP was almost one-fourth. The high grade of the colposcopic directed biopsy histology was a significant factor associated with having positive margins.

Keywords: positive margin, loop electrosurgical excision procedure, preinvasive squamous cell carcinoma, cervical intraepithelial neoplasia, carcinoma of cervix.

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ความชุกและปัจจัยที่เกี่ยวข้องกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้า

รวิสรา จำปาวงค์, เสาวณีย์ ตั้งมโนวุฒิกุล, สุรพงศ์ แสนโภชน์, ศรีสุดา ทรงธรรมวัฒน์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักคือเพื่อศึกษาความชุกของการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าเป็นรูปกรวย และวัตถุประสงค์รองเพื่อศึกษาปัจจัยที่เกี่ยวข้อง*

วิธีการวิจัย: *ศึกษาข้อมูลย้อนหลังของผู้ป่วยที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้าในโรงพยาบาลอุดรธานี ตั้งแต่ เดือนมีนาคม 2559 ถึง เดือนกรกฎาคม 2561 จำนวน 350 คน ทำการบันทึกข้อมูลได้แก่ ข้อมูลพื้นฐาน, ผลตรวจคัดกรองมะเร็งปากมดลูก, ผลการส่องกล้องตรวจปากมดลูก, ผลชิ้นเนื้อจากการตัดปากมดลูกขณะส่องกล้องตรวจปากมดลูก, ผลชิ้นเนื้อปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าและรอยโรคที่ขอบชิ้นเนื้อ นำข้อมูลมาวิเคราะห์หาความชุกและปัจจัยที่มีความสัมพันธ์กับการตรวจพบรอยโรคที่ขอบชิ้นเนื้อปากมดลูก*

ผลการวิจัย: *ในช่วงเวลาดังกล่าวมีผู้ป่วยที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้าและข้อมูลครบถ้วนจำนวน 323 คน อายุเฉลี่ย 42.3 ปี ส่วนใหญ่ของผู้ป่วยมีดัชนีมวลกาย < 30 kg/m^2 (304 คน หรือ ร้อยละ 94.1) ไม่เป็นผู้ติดเชื้อ HIV (295 คน หรือ ร้อยละ 91.3) และยังมีประจำเดือน (246 คน หรือ ร้อยละ 76.2) ผู้ป่วยที่มีรอยโรคที่ขอบชิ้นเนื้อมีจำนวน 80 คน (ร้อยละ 24.8) ส่วนใหญ่เป็นรอยโรคที่ขอบชิ้นเนื้อด้านใน ร้อยละ 48.8 โดยปัจจัยที่เกี่ยวข้องอย่างมีนัยสำคัญทางสถิติกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าคือ ผลชิ้นเนื้อปากมดลูกจากการส่องกล้องตรวจปากมดลูกรุนแรงกว่าระดับ cervical intraepithelial neoplasia 2 โดยพบว่า adjusted odds ratio เท่ากับ 3.91 (ระดับความเชื่อมั่นร้อยละ 95% คือ 1.35-11.27)*

สรุป: *พบความชุกของการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าประมาณหนึ่งในสี่ของผู้ป่วย โดยปัจจัยที่มีผลกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อปากมดลูกได้แก่ ผลพยาธิวิทยาจากการส่องกล้องตรวจปากมดลูกที่มีความรุนแรงกว่าระดับ CIN 2*

คำสำคัญ: *การตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อ, การตัดปากมดลูกด้วยห่วงไฟฟ้า, มะเร็งปากมดลูกระยะยังไม่มีการรุกราน, ระยะก่อนมะเร็งของปากมดลูก, มะเร็งปากมดลูก*

Introduction

Cervical cancer is the third most common cause of death for woman in developing countries[1] and the second highest incidence of cancer in Thailand[2]. Cervical cancer is a preventable cancer because it takes a long time to progress from normal cervical epithelium to precancerous lesion and finally becoming an invasive pattern. Pap smear has been used effectively for screening and detection of the precancerous lesions of the cervix following the Bethesda system[3]. Cervical intraepithelial neoplasia (CIN) is frequently diagnosed and treated by cervical conization according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guideline for managing abnormal cervical cancer screening tests and cancer precursors (2012)[4].

Cervical conization can be performed using either cold-knife conization (CKC), loop electrosurgical excision procedure (LEEP) or laser conization. LEEP is widely used, because it can be performed in an outpatient setting, minimal bleeding, cost-effective and its results are comparable with the CKC and laser conization[5]. However, a common problem with LEEP is the positive margin of cervical tissue specimen which is a risk for persistence or recurrence of cervical dysplasia that can progress to squamous cell carcinoma[6]. Management of positive margin is controversial, including follow-up with cytology, endocervical sampling, re-excision or hysterectomy if it cannot be re-excised[4, 7].

Many studies have reported the prevalence of positive margin after LEEP, varying from 12.3 to 47.0% and inconclusive associated factors[8-15]. Therefore, the primary objective was to find the prevalence of positive margins of cervical tissue from LEEP for conization and the secondary objective was to determine its associated factors. This knowledge will be used by the gynecologists for awareness of high risk cases in the patient's treatment and follow-up process.

Materials and Methods

This study was a retrospective descriptive study. After the study protocol was approved by Udonthani Research Ethics Committee, the medical records were reviewed. The inclusion criteria was patients who underwent LEEP for indications according to ASCCP guideline at the Department of Obstetrics and Gynecology, Udonthani Hospital, Thailand, from March 2016 to July 2018. According to the ASCCP guideline, colposcopy was done in case of cervical cancer screening test was positive for abnormal cervical cytology ≤ LSIL and high risk HPV type 16 and 18. LEEP conization was done without colposcopy in case of abnormal cervical cytology ≥ HSIL who age ≥ 25 years. The sample size was calculated by the formula for a descriptive study using the estimated prevalence of positive margin after LEEP of 14.3%[8, 16], a 5% chance of making a type 1 error and acceptable error of 5%. One hundred and eighty nine women were needed for the study.

Baseline characteristics were recorded which included age, body weight, height, parity, menstrual status, human immunodeficiency virus (HIV) status, history of smoking and level of surgeon. Other information included the women's pathologic information, preoperative cytology, colposcopic finding, preoperative histology, LEEP histology and surgical margin. The exclusion criteria was incomplete data of patient's medical records.

The statistical analysis was performed using Stata version 13. Continuous variables were presented by the mean ± standard deviation. Categorical variables were presented by number and percentage. The chi-square test, Fisher exact or student t-test were performed to evaluate the discrete variables. The associated factors of positive margin were evaluated by multivariate logistic regression, and were presented as odd ratios (ORs) with 95% confidence intervals (95%CI). A p value < 0.05 was considered statistically significant.

Results

From March 2016 to July 2018, there were 350

women who underwent LEEP at the Department of Obstetrics and Gynecology, Udonthani Hospital, Thailand. Twenty seven of these women were excluded from the study because of incomplete data. A total of 323 patient's records were analyzed. Baseline characteristics are shown in Table 1. The mean age was 42.3±10.6 years, mean body weight was 56.5±9.5 kilograms (kg), mean height was 155.5±8.6 centimeters (cm) and mean body mass index (BMI) was 23.9±10.9 kg/m^2. Most patients had a BMI < 30 (n = 304; 94.1%) and were multiparous (n = 287; 88.8%), HIV negative (n = 295; 91.3 %) and premenopausal status (n = 246; 76.2%).

Preoperative cytology is presented in Table 2. Most patients had high grade squamous intraepithelial lesion (HSIL) (51.4%). A Colposcopy was done in 169 patients (52.3%) with 78 patients (46.2%) having an unsatisfied colposcopic finding and 91 patients (53.8%) having a satisfied colposcopic finding. A total of 118 patients were colposcopic directed biopsy, preoperative histology are presented in Table 2.

Postoperative histology is presented in Table 3. Most patients had cervical intraepithelial neoplasia (CIN) 3 (43.6%). The prevalence of positive margins of cervical tissue form LEEP was found in 80 cases (24.8%), the most positive margin site was endocervix (48.8%). Data of preoperative associated factors are presented in Table 4 as positive and negative margin groups. Univariate and multivariate logistic regression analysis was done in possibly associated factors with positive margins as shown in Table 4. A significant characteristic was colposcopic directed biopsy histology > CIN 2 with the adjusted ORs of 3.91 (95%CI 1.35-11.27).

Table 1. Baseline characteristics.

Characteristics	Total (N=323)	$^+$ve magin (N=80)	$^-$ve margin (N=243)	p value
Age (years), mean±SD	42.3±10.6	43.3±10.7	42.0±10.6	0.34
BW (kg), mean±SD	56.5±9.5	57.8±10.0	56.1±9.3	0.18
Height (cm), mean±SD	155.5±8.6	155.5±6.4	155.5±9.2	0.99
BMI (kg/m^2), mean±SD	23.9±10.9	23.9±3.8	23.9±12.4	0.98
- BMI < 30	304(94.1%)	74(24.3%)	230(75.7%)	0.48
- BMI ≥ 30	19(5.9%)	6(31.6%)	13(68.4%)	0.48
Nulliparous	36(11.2%)	9(25%)	27(75%)	0.97
Postmenopause	77(23.8%)	22(28.6%)	55(71.4%)	0.38
Anti HIV +ve	28(8.7%)	10(35.7%)	18(64.3%)	0.16
Level of surgeon				
Resident	122(37.8%)	38(31.1%)	84(68.9%)	0.04
Staff	201(62.2%)	42(20.9%)	159(79.1%)	

Data are presented in term of N (%) unless specified otherwise

- p value was calculated by student's t test for continuous data and Pearson chi square or Fisher exact test for categorical data
- $^+$ve: positive, $^-$ve: negative, SD: standard deviation, BW: body weight, BMI: body mass index, HIV: human immunodeficiency virus.

Table 2. Preoperative cytology and histology.

Characteristics	Total (N=323)	+ve magin (N=80)	-ve margin (N=243)	p value
Cervical cytology*				
+ve HPV 16 or 18	10 (3.1%)	3 (30%)	7 (70%)	0.70
ASC-US	39 (12.0%)	6 (15.4%)	33 (84.6%)	0.15
LSIL	34 (10.5%)	6 (17.6%)	28 (82.4%)	0.31
ASC-H	49 (15.1%)	9 (18.4%)	40 (81.6%)	0.26
HSIL	166 (51.2%)	46 (27.7%)	120 (72.3%)	0.21
SCCA	7 (2.2%)	3 (42.9%)	4 (57.1%)	0.26
AGC	13 (4.0%)	4 (30.8%)	9 (69.2%)	0.61
AIS	6 (1.9%)	3 (50%)	3 (50%)	0.15
Staff				
Colposcopic finding				
Not done	154 (47.7%)	45 (29.2%)	109 (70.8%)	0.17
Satisfied	91 (28.2%)	17 (18.7%)	74 (81.3%)	
Unsatisfied	78 (24.2%)	18 (23.1%)	60 (76.9%)	
Colposcopic directed biopsy histology**				
Not done	205 (63.1%)	53 (25.9%)	152 (74.1%)	0.04
No CIN	2 (0.6%)	0	2 (100%)	
CIN 1	15 (4.6%)	0	15 (100%)	
CIN 2	36 (11.1%)	6 (16.7%)	30 (83.3%)	
CIN 3	44 (13.5%)	16 (36.4%)	28 (63.6%)	
CIS	17 (5.2%)	4 (23.5%)	13 (76.5%)	
AIS	6 (1.8%)	5 (83.3%)	1 (16.7%)	

Data are presented in term of N (%) unless specified otherwise.

- +ve: positive, -ve: negative, HPV: Human papilloma virus, ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells cannot exclude HSIL, HSIL: High grade squamous intraepithelial lesion, AGC: Atypical glandular cells, SCCA: Squamous cell carcinoma, AIS: Adenocarcinoma in situ, CIN: Cervical intraepithelial neoplasia, CIS: Carcinoma in situ

* 1 case of HSIL with AIS

**1 case of CIN 3 with AIS, 1 case of CIS with AIS

Table 3. Postoperative histology.

Characteristics	Total	$^{+}$ve margin	$^{-}$ve margin	p value
LEEP pathology*				
No CIN	29 (8.9%)	0	29 (100%)	< 0.01
CIN 1	24 (7.4%)	6 (25.0%)	18 (75.0%)	
CIN 2	47 (14.4%)	12 (25.5%)	35 (74.5%)	
CIN 3	142 (43.6%)	40 (28.2%)	102 (71.8%)	
CIS	62 (19.0%)	9 (14.5%)	53 (85.5%)	
AIS	11 (3.4%)	5 (45.5%)	6 (54.5%)	
SCCA	9 (2.8%)	6 (66.7%)	3 (33.3%)	
Adenocarcinoma	2 (0.6%)	2 (100%)	0	
Type of $^{+}$ve margin				
Endocervix		39 (48.8%)		
Ectocervix		21 (26.3%)		
Both		18 (22.5%)		
Not specified		2 (2.5%)		

Data are presented in term of N (%) unless specified otherwise.

- $^{+}$ve: positive, $^{-}$ve: negative, LEEP: loop electrosurgical excision procedure, CIN: Cervical intraepithelial neoplasia, CIS: Carcinoma in situ, AIS: Adenocarcinoma in situ, SCCA: Squamous cell carcinoma

* 3 cases of CIS with AIS

Table 4. Preoperative associated factors of positive margin of LEEP specimen.

Factors	$^{+}$ve margin (N=80)	$^{-}$ve margin (N=243)	Crude OR (95%CI)	Adjusted OR (95%CI)	p value
Age (years), mean±SD	43.3±10.7	42.0±10.6	1.01 (0.99-1.04)	1.00 (0.94-1.07)	0.79
BMI (kg/m^2), mean±SD	23.9±3.8	23.9±12.4	1.00 (0.98-1.02)	1.00 (0.95-1.04)	0.86
Nulliparous	9 (25.0%)	27 (75.0%)	1.01 (0.46-2.26)	0.67 (0.16-2.84)	0.59
Postmenopause	22 (28.6%)	55 (71.4%)	1.30 (0.73-2.31)	0.78 (0.16-3.84)	0.76
HIV positive	10 (35.7%)	18 (64.3%)	1.78 (0.78-4.05)	1.33 (0.25-6.92)	0.74
Level of surgeon					
Resident	38 (31.1%)	84 (68.9%)	1.71 (1.03-2.86)	1.60 (0.59-4.35)	0.36
Staff	42 (20.9%)	159 (79.1%)			
Preoperative cytology*					
≤ LSIL	15 (18.1%)	68 (81.9%)	1.68 (0.90-3.15)	1.06 (0.42-2.69)	0.91
> LSIL	65 (27.0%)	176 (73.0%)			
Colposcopic directed biopsy histology**					
≤ CIN2	6 (11.3%)	47 (88.7%)	3.74 (1.38-10.12)	3.91 (1.35-11.27)	0.01
> CIN2	25 (37.3%)	42 (62.7%)			

- LEEP: loop electrosurgical excision procedure, +ve: positive, -ve: negative, ORs: odds ratio, SD: standard deviation, BMI: body mass index, HIV: human immunodeficiency virus, LSIL: Low grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia

*1 case of HSIL with AIS, **1 case of CIN 3 with AIS, 1 case of CIS with AIS

Discussion

Prevalence of positive margin of cervical tissue form LEEP at Udonthani Hospital was 24.8% which was similar to 12.3-44.0% from the other studies. For example, Chen, et al reported 35.8% of positive margin at Jining No.1 People's Hospital, China[9]. Kietpeerakool, et al reported 44.0% of positive margin at Chiang Mai University Hospital[11]. Panna, et al reported 12.3% of positive margin at Srinangarind Hospital[14]. Tanompongchat, et al reported 35.3% of positive margin at Siriraj Hospital[15]. These results were varied by the characteristics of study population, hospitals, surgeons and histological type.

In this study, the associated factor of positive margin of cervical tissue form LEEP was colposcopic directed biopsy histology > CIN 2 which was similar to Chaijindaratana, et al[8] and Panna, et al[14] studies. The reason of higher risk of positive margin in this group was the greater degree of pathology might have more extension of disease. However, this study did not found the association of positive margin with nulliparous, age or post menopause that might affect the transformation zone of cervix which were reported in Chaijindaratana, et al[8] Chen, et al[10] and Tanompongchat, et al studies[15]. The skill and experience of surgeon was also reported as the associated factors in Chaijindaratana, et al[8] and Panna, et al[14] studies, which was not found in this study. Others associated factors, such as human papilloma virus (HPV) positive, history of HIV, history of smoking that might interfere the immunological factor were also reported in previous studies[8, 9, 12]. However, these were not found in this study. The reason of difference might be from the different population, surgeons and also the sample size of study which had small cases in some factors such as history of HIV or nulliparous.

The clinical application of this study is for the gynecologists to be concerned about the positive margin of LEEP specimen especially in the high grade preoperative histology. The top hat of LEEP might be needed in the > CIN 2 case to reduce the positive endocervical margin which was found in more than one-third of case compared with 11.3% in the ≤ CIN 2. The wider cervical tissue specimen might also be needed in this situation to avoid positive ectocervical margin. However, multiple factors such as size, amount of lesion and colposcopic finding should be considered to avoid excessive surgery and increased complications. The limitation of this study was the retrospective data collection which some associated factors were not collected such as site, quadrant, size of lesion and the size of cervical tissue specimens. The postoperative histology and surgical margins were also reported by many pathologists and this might cause some variation in diagnosis. Moreover, colposcopy was not done in many cases in this study due to the ASCCP guideline which treated abnormal cervical cytology > HSIL by LEEP without colposcopy.

Conclusion

The prevalence of positive margins of cervical tissue form LEEP was almost one-fourth. The high grade colposcopic directed biopsy histology was a significant factor associated with the positive conization margins.

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Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Respiratory Distress in Early Premature Newborns with Suboptimal Antenatal Steroid

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ABSTRACT

Objectives: To study the effects between a complete course and an incomplete course of dexamethasone on the incidence of respiratory distress syndrome in newborn infants aged below 34 weeks.

Materials and Methods: A retrospective cohort study was conducted on 118 pregnant patients at 24-33^{+6} weeks of gestation. The sample was divided into two groups: the first group consisting of 63 pregnant patients who received an incomplete course of dexamethasone (< 4 doses) prior to delivery and the second group comprising 55 pregnant patients who received a complete course of dexamethasone prior to delivery (within 14 days after the first dose). Data were collected from electronic medical records to obtain information about the baseline characteristics of the sample, the number of doses of dexamethasone received, the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early-onset neonatal sepsis (EOS), and neonatal death.

Results: The rates of RDS incidence and neonatal death amongst pregnant patients who received a complete course of dexamethasone significantly decreased from 74.6% to 50.9% (AOR, 0.37; 95%CI, 0.17-0.84) and from 12.7% to 1.8% (AOR, 0.10; 95%CI, 0.01-0.98), respectively, when compared with pregnant patients who received an incomplete course of dexamethasone. Alternatively, there were no statistically significant differences between the two groups in terms of the incidence of IVH, NEC, patent ductus arteriosus (PDA), NICU admission within the first 7 days of birth, and surfactant requirement. Meanwhile, the incidence rate of EOS increased from 19% to 26.5% (AOR, 3.18; 95%CI, 1.13-8.97).

Conclusion: The administration of a complete course of dexamethasone to pregnant patients with gestational age of less than 34 weeks is conducive to a decrease in the incidence of RDS and neonatal death, while contributing to an increased incidence of EOS.

Keywords: respiratory distress syndrome, dexamethasone, incomplete course.

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การเกิดภาวะหายใจลำบากในทารกแรกเกิดที่คลอดก่อนกำหนดและได้รับยา dexamethasone ไม่ครบ

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาภาวะหายใจลำบากในทารกแรกเกิดที่คลอดอายุครรภ์น้อยกว่า 34 สัปดาห์ ที่ได้ dexamethasone ครบ 4 เข็ม เปรียบเทียบกับ dexamethasone ไม่ครบ 4 เข็ม*

วัสดุและวิธีการ: *เป็นการศึกษาวิจัยจากเหตุไปหาผลแบบย้อนหลัง ในสตรีตั้งครรภ์ 24-33^{+6} สัปดาห์ จำนวนทั้งหมด 118 คน ศึกษาสองกลุ่ม กลุ่มแรกได้ dexamethasone ไม่ครบสี่เข็ม มีจำนวน 63 คน และกลุ่มที่สองได้ dexamethasone ครบสี่เข็ม เป็นจำนวน 55 คน เก็บบันทึกข้อมูลจากเวชระเบียนอิเล็กทรอนิกส์ ได้แก่ ข้อมูลพื้นฐานประชากร จำนวนเข็มของ dexamethasone ก่อนคลอด ภาวะหายใจลำบากในทารกแรกเกิด และอัตราการพิการอื่น เช่น ภาวะเลือดออกในโพรงสมอง ภาวะลำไส้อักเสบชนิดเนื้อตาย ภาวะติดเชื้อในทารกแรกเกิด อัตราการเสียชีวิต*

ผลการศึกษา: *ผลการศึกษาพบว่ากลุ่มมารดาที่ได้ dexamethasone ครบ 4 เข็ม เปรียบเทียบกับ ได้ dexamethasone ไม่ครบ 4 เข็ม มีภาวะหายใจลำบากในทารกแรกเกิดลดลงร้อยละ 74.6 เป็นร้อยละ 50.9 (AORs 0.37; 95%CI 0.17-0.84) และอัตราการเสียชีวิตของทารกลดลงร้อยละ 12.7 เหลือร้อยละ 1.8 (AORs 0.10; 95%CI 0.01-0.98) ส่วนภาวะเลือดออกในโพรงสมอง ภาวะลำไส้อักเสบชนิดเนื้อตาย การเข้า NICU ใน 7 วันแรก ภาวะโรคหัวใจพีดีเอ ภาวะต้องการ surfactant หลังคลอดไม่แตกต่างกัน แต่ภาวะติดเชื้อแรกเกิดมีการเพิ่มขึ้น (AORs 3.18, 95%CI 1.13-8.97)*

สรุป: *การได้ dexamethasone ในผู้หญิงตั้งครรภ์น้อยกว่า 34 สัปดาห์ ครบ 4 เข็ม มีประโยชน์ในเรื่อง ภาวะหายใจลำบากในทารกแรกเกิดที่ลดลง และอัตราการเสียชีวิตที่ลดลง แต่การศึกษานี้มีข้อควรระวังเรื่องการได้ steroids ครบ มีภาวะติดเชื้อทารกแรกเกิดเพิ่มขึ้น*

คำสำคัญ: *ภาวะหายใจลำบากในทารกแรกเกิด, Dexamethasone, ไม่ครบสี่เข็ม*

Introduction

According to the 2005 report[1] of the World Health Organization, there were approximately 12.9 million (9.6%) women delivering preterm with the preterm neonatal mortality rate being 35%. Indeed, the rate of preterm birth is found to be gradually increased every year as evident in the 2010 statistical report[2], which indicates that the rate of preterm birth has increased to 11.1%. At Maharat Nakhon Ratchasima Hospital, the incidence rate of preterm birth during October 2012 to September 2015 was 21.15% per year on average.

Preterm birth is the leading cause of various health complications and significantly contributes to the high incidence of death and disability amongst preterm infants. Hence, it is considered a major national problem that should be addressed and resolved, both in the aspects of prevention and treatment. As of present, Thailand has prescribed a guideline[3] for treatment of fetuses at risk of preterm birth. The guideline encompasses: 1) optimization of fetal development if there are no signs of contraindications and 2) administration of a complete course of antenatal steroids, specifically dexamethasone, at 24-33^{+6} weeks of pregnancy to reduce morbidity and mortality. It has been reported[4] that the administration of antenatal steroids can reduce the incidence of perinatal death, neonatal death, respiratory distress syndromes (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and systemic infections, as well as the need for mechanical ventilation in the first 48 hours of life. Nonetheless, the administration of antenatal steroids is often not feasible due to unsuccessful inhibition of preterm birth or indications of labor such as pregnancy complications or poor fetal health, which leads to an incomplete course of antenatal steroids. Regarding the effectiveness of an incomplete course of antenatal steroids, the ACOG[5] (2006) stated that: "the administration of antenatal steroids within 24 hours of delivery can significantly reduce the rate of neonatal mortality and complications, even at one dose of 6 mg". Similarly, one meta-analysis[6] study reported that the administration of the first course of antenatal steroids within 24 hours of delivery can reduce the incidence of RDS.

Concerning the side effects of antenatal steroids, it has been reported[4,7] that a complete course of antenatal steroids has no short-term side effects that are of statistical significance, particularly in the aspect of mortality rate, birth weight, and infection rate. Moreover, there is no evidence of long-term side effects[4,7-11] relating to nervous system or cognitive functions.

Maharat Nakhon Ratchasima Hospital is a referral hospital that supports patients who are transferred from other provincial hospitals, including those located in Regional Health 9 that have a large number of pregnant women at risk of preterm birth. Regarding the fact that there are very few studies conducted on an incomplete course of dexamethasone, the researcher is interested in studying the effects of an incomplete course of dexamethasone. The findings of this research will facilitate physicians to make decisions, treatment plans, and prognosis in a more effective manner.

Materials and Methods

This research was a retrospective cohort study approved by the Research Ethics Committee of Maharat Nakhon Ratchasima Hospital. The research was conducted on 118 singleton pregnant patients with gestational age of 24 to 33^{+6} weeks who delivered at Maharat Nakhon Ratchasima Hospital during April 1, 2010 to March 31, 2016. The sample was divided into two groups: the first group consisting of 63 pregnant patients who received an incomplete course of dexamethasone (< 4 doses) prior to delivery and the second group comprising 55 pregnant patients who received a complete course of dexamethasone prior to delivery (within 14 days after the first dose). The exclusion criteria were no prenatal care, intraamniotic infection, severe congenital anomalies or thoracic malformation, administration of a rescue course, and dexamethasone regimen other than 6 mg intramuscular every 12 hours.

The sample size was determined from a pilot study conducted on 20 pregnant patients, and the principles of the "comparison of two independent proportions" were adopted. Based on the equation, $N = \{2(Z\alpha + Z\beta)^2\ p(1 - p)\}/(p1 - p2)^2$, the minimum sample size for a single proportion was 45 or an equivalent of 90 for two independent proportions. Data were collected from the data collection system of Maharat Nakhon Ratchasima Hospital, which consisted of: age, gravidity, weight, height, number of doses of dexamethasone received before delivery, indications for preterm delivery prior to the administration of a complete course of dexamethasone, gestational age at birth, incidence of rupture of membranes, labor pain, fetal distress, pregnancy complications, method of delivery, birth weight, incidence of asphyxia, predelivery administration of antibiotics, incidence of neonatal complications, RDS, IVH, NEC, neonatal death, early-onset neonatal sepsis (EOS), NICU admission within the first 7 days of birth, and pre-discharge mortality status.

The obtained data were statically analyzed with Stata Version 13 software and statistical tests, namely chi-square test, Fisher's exact test, and t-test, depending on the type of variables. The results were considered statistically significant when p value < 0.05. Moreover, confounding variables were controlled by adjusted odds ratios that had a magnitude of more than 10 percent.

Results

There were 118 pregnant patients who delivered at Maharat Nakhon Ratchasima Hospital during April 1, 2010 to March 31, 2016. Across the sample of 118 pregnant patients, 63 received an incomplete course of dexamethasone and 55 received a complete course of dexamethasone.

Regarding the baseline characteristics of the sample, as illustrated in Table 1, there were statistically significant differences between the two groups in terms of method of delivery, incidence of pregnancy induced hypertension, oligohydramnios, rupture of membranes, labor pain, and fetal distress. Alternatively, there were no statistically significant differences between the two groups in term of mother's age, gestational age, gravidity, mother's weight and height, birth weight, infant gender, small for gestational age newborns, predelivery administration of antibiotics, and mother's pre-existing conditions.

The treatment outcomes of pregnant patients who received complete a course of dexamethasone were compared with those who received an incomplete course of dexamethasone. According to the results, there were statistically significant decreases in the rate of RDS from 74.6% to 50.9% (AORs 0.37; 95%CI 0.17-0.84) and the rate of neonatal deaths (AORs 0.10; 95%CI 0.01-0.98). On the other hand, no statistically significant differences were observed with respect to the incidence of IVH (AORs 0.47; 95%CI 0.08-2.82), incidence of NEC (AORs 0.61; 95%CI 0.17-2.14), NICU admission within the first 7 days of birth (AORs 1.04; 95%CI 0.43-2.53), incidence of PDA (AORs 0.76; 95%CI 0.32-1.83), and surfactant requirement (AORs 0.91; 95%CI 0.66-1.26). Meanwhile, there was a statistically significant increase in the incidence of EOS from 19% to 36.4% (AORs 3.18; 95%CI 1.13-8.97), as illustrated in Table 2.

After comparing the treatment outcomes between 1 and 4 doses, 2 and 4 doses, and 3 and 4 doses of dexamethasone administered, the odds ratios were 0.39 (95%CI 0.16-0.97), 0.19 (95%CI 0.05-0.70), and 0.59 (95%CI 0.17-2.14), respectively, as shown in Table 3.

According to Table 2, the administration of a complete course of antenatal steroids was found to increase the incidence rate of EOS. Hence, the odds ratios were adjusted to predict the confounding variables that may have influence on both dependent and independent variables. From Table 4, the contributing factors to the incidence of EOS were fetal distress (ORs 4.71; 95%CI 1.10-20.07) and administration of a complete course of antenatal steroids (ORs, 2.19; 95%CI 1.13-8.97). Meanwhile, the protective factors of EOS were labor pain (ORs 0.21; 95%CI 0.10-0.44) and cesarean section (ORs

0.34; 95%CI 0.14-0.86). Regarding the incidence of rupture of membranes, no statistically significant differences were observed (ORs 0.62; 95%CI 0.21-1.89).

Table 1. Baseline characteristics.

	Incomplete antenatal steroids n = 63	Complete antenatal steroids n = 55	p value
Maternal ages (years), mean	26.58	27.89	0.327
Gestations			0.509
Primigravida, n (%)	29 (46.03)	22 (40.00)	
Multigravida, n (%)	34 (53.97)	33 (60.00)	
Gestational ages (weeks)			0.077
$24\text{-}27^{+6}$, n (%)	12 (19.05)	3 (5.45)	
$28\text{-}31^{+6}$, n (%)	25 (39.68)	28 (50.91)	
$32\text{-}33^{+6}$, n (%)	26 (41.27)	24 (43.64)	
Heights (cm)	157.84	157.78	0.959
Body weights (kg)	63.84	68.24	0.120
Route of delivery			0.003*
Cesarean section, n (%)	40 (63.50)	48 (87.5)	
Vaginal route, n (%)	23 (36.50)	7 (12.5)	
Gender fetus			0.777
Male, n (%)	36 (57.14)	30 (54.55)	
Female, n (%)	27 (42.86)	25 (45.45)	
Birth weight (g), mean	1,532	1,593	0.468
Pregnancy induced hypertension, n (%)	17 (26.98)	25 (45.45)	0.037*
Intrauterine growth restriction, n (%)	8 (12.70)	3 (5.45)	0.216
Oligohydramnios, n (%)	5 (7.94)	20 (36.36)	< 0.001*
Received antibiotic, n (%)	32 (50.79)	30 (54.55)	0.684
Rupture of membanes, n (%)	9 (14.29)	20 (36.36)	0.005*
Labor pain, n (%)	45 (71.43)	28 (50.91)	0.022*
Fetal distress, n (%)	15 (23.81)	2 (3.64)	0.003*
APGAR at 1 min (mean)	6.84	7.46	0.169[t]
APGAR at 5 mins (mean)	8.71	9.23	0.153[t]
Medical complications[K], n (%)	17 (26.98)	20 (36.36)	0.273

* Statistical significance

[t] "T test mean different"

[K] Medical complications include heart disease, lung disease, kidney disease, thyroid disease, chronic hypertension, autoimmune disease, HIV infection, multiple trauma

Table 2. Outcome of complete course (compared with incomplete course).

	Complete antenatal steroids n = 55	Incomplete antenatal steroids n = 63	Crude ORs (95%CI)	Adjusted ORs[#] (95%CI)
Primary outcome				
RDS[r]	28 (50.9)	47 (74.6)	0.35 (0.16-0.76)*	0.37 (0.17-0.84)*
Secondary outcome				
IVH[I]	2 (3.6)	4 (6.3)	0.56 (0.00-2.73)	0.47 (0.08-2.82)
NEC[N]	6 (10.9)	11 (17.5)	0.58 (0.21-1.64)	0.61 (0.17-2.14)
EOS[E]	20 (36.4)	12 (19.0)	2.43 (1.06-5.54)*	3.18 (1.13-8.97)*
NICU7[N]	15 (27.3)	20 (31.7)	0.81 (0.37-1.77)	1.04 (0.43-2.53)
PDA[P]	15 (27.3)	24 (38.1)	0.61 (0.28-1.32)	0.76 (0.32-1.83)
Death[D]	1 (1.8)	8 (12.7)	0.13 (0.00-0.82)*	0.10 (0.01-0.98)*
Need surfactant[S]	7/28 (25)	17/47 (36.2)	0.59 (0.21-1.64)	0.91 (0.66-1.26)

* Statistical significance; incomplete antenatal steroids was reference. (Odds ratio = 1)

[#] Adjusted odd ratio was controlled by confounding variables that had a magnitude change more than 10%.

[r] Respiratory distress syndrome was adjusted by cesarean section (C/S), labor pain; [I] Intraventricular hemorrhage was adjusted by pregnancy induced hypertension (PIH); [N] Necrotizing enterocolitis was adjusted by oligohydramnios, PIH, and fetal distress; [E] Early-onset neonatal sepsis was adjusted by labor pain, fetal distress, rupture of membranes (ROM) and C/S; [N] NICU admission within the first 7 days of birth was adjusted by oligohydramnios and fetal distress; [P] Patent ductus arteriosus was adjusted by oligohydramnios, C/S and fetal distress; [D] Neonatal death was adjusted by oligohydramnios, ROM and C/S; [S] Need for surfactant in RDS neonates was adjusted by labor pain and PIH.

Table 3. The relation of number of each incomplete doses with complete doses of dexamethasone.

	Complete antenatal steroids n = 55	Incomplete antenatal steroids n = 63	Odds ratio (95%CI)
RDS outcome			
1 dose vs 4 doses	28 (50.91)	24 (72.73)	0.39 (0.16-0.97)*
2 doses vs 4 doses	28 (50.91)	16 (84.21)	0.19 (0.05-0.70)*
3 doses vs 4 doses	28 (50.91)	7 (63.64)	0.59 (0.17-2.14)

* Statistical significance; incomplete antenatal steroids was reference. (Odds ratio = 1)

Table 4. Risk factors of early-onset neonatal sepsis.

Risk factors of EOS	Odds ratio	95%CI
Complete antenatal steroids	3.19	(1.13-8.97)*
Fetal distress	4.71	(1.10-20.07)*
Labor pain	0.21	(0.10-0.44)*
Rupture of membranes	0.62	(0.21-1.89)
Cesarean section	0.34	(0.14-0.86)*

* Statistical significance

Discussion

The administration of a complete course of antenatal steroids to pregnant patients with gestational age less than 34 weeks has been reported to be beneficial to newborn infants, both in the aspect of morbidity and mortality. Furthermore, the administration of antenatal steroids can reduce the incidence rate of RDS, which applies to both complete and incomplete courses of antenatal steroids. According to the results of this research, the incidence rate of RDS after administration a complete course of dexamethasone significantly decreased from 74.6% to 50.9% (AORs 0.37; 95%CI 0.17-0.84) when compared with the administration of an incomplete course of dexamethasone. These results were similar to the previous study of Kumar TR[12], which was conducted on the administration of dexamethasone to NICU admitted infants and infants aged below 35 weeks. The sample was divided into 3 groups: the first group was given a complete course of dexamethasone, the second group was given an incomplete course of dexamethasone, and the third group did not receive treatment. The results indicated that the incidence rate of RDS amongst infants in the first group decreased from 61.6% to 36.3% (ORs 0.36; 95%CI 0.14-0.94) when compared with the second group. Alternatively, the previous study of Chen-Yu Chen[13], which examined the treatment outcomes between the predelivery administration of dexamethasone and betamethasone, showed that there were no statistically significant differences in terms of RDS, severe IVH, NEC, and neonatal sepsis. Nonetheless, the studies found that the incidence rate of RDS after administration of a complete course of antenatal steroids significantly reduced from 68.6% to 48.4% (ORs 0.42; 95%CI 0.20-0.94) when compared with the administration of an incomplete course of antenatal steroids.

In addition, this research found that there were no statistically significant differences in terms of the incidence of IVH, NEC, and surfactant requirement. These results were consistent with previous studies of Chen-Yu Chen[13] and Kumar TR[12]. As for NICU admission within the first 7 days of birth, there were no previous studies for comparison. Concerning the fact that these results were secondary outcomes, the sample size was insufficient to determine the statistical significance of the results.

With respect to the incidence of EOS, a statistically significant increase in the incidence rate was observed (ORs 3.18; 95%CI 1.13-8.97). This was inconsistent with the previous study[13], which found no statistically significant differences (ORs 1.50; 95%CI 0.43-5.10). Furthermore, this research found that the contributing factors to the incidence of EOS were administration of a complete course of dexamethasone and fetal distress, while the protective factors were cesarean section and labor pain. Concerning the incidence of rupture of membranes, there were no statistically significant differences. Further studies are needed to substantiate this finding.

Concerning the rate of neonatal deaths, a statistically significant decrease in the death rate was observed (ORs 0.10; 95%CI 0.01-0.98). This was consistent with the previous study of Kumar TR[12], which found that the rate of neonatal deaths decreased from 10.7% to 0%. According to this research, the effectiveness of dexamethasone was statistically significant after at least 24 hours of administration (first or second dose and forth dose). This was similar to the previous meta-analysis study[6], which found that antenatal steroid was effective after 24 hours of administration (after second dose). These results could be beneficial for treatment of pregnant patients whose conditions are difficult for making decisions, specifically whether or not the administration of dexamethasone should be delayed until 24 hours before delivery in order to optimize the effectiveness of treatment.

The strength of this research was sufficient sample size, since data were collected from a referral hospital. Meanwhile, the limitation of this research was the fact that data were collected retrospectively. Hence, the confounding variables could not be determined. However, this limitation was mitigated by adjusting the odds ratios for confounding variables.

Conclusion

The administration of a complete course of dexamethasone to pregnant patients with gestational age less than 34 weeks was found to reduce the rates of RDS and neonatal death. Accordingly, it is recommended to administer antenatal steroids to all pregnant patients at risk of preterm birth, provided that there are no contraindications and conditions for emergency childbirth. In addition, a complete course of antenatal steroids should be administered to optimize the effectiveness of treatment. However, this research suggested that a complete course of antenatal steroids should be administered with caution due to its effect on the incidence of EOS.

Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Subsequence Pregnancy Outcomes after Treatment of Gestational Trophoblastic Disease in King Chulalongkorn Memorial Hospital

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ABSTRACT

Objectives: To review subsequent pregnancy outcome in gestational trophoblastic disease (GTD) patients at King Chulalongkorn Memorial hospital.

Materials and Methods: Retrospective cohort study was done between 2001 and 2015. Women whom diagnosed with gestational trophoblastic disease at King Chulalongkorn Memorial Hospital, Bangkok, Thailand were recruited. Data were reviewed by medical record and telephone interview regarding subsequent pregnancy outcome and clinical data.

Results: There were 147 GTD patients enrolled during study period, 82 pregnant women were observed. Final diagnosis was complete hydatidiform mole 40 cases (48.78%), partial hydatidiform mole 11 cases (13.41%), postmolar gestational trophoblastic neoplasia 28 cases (34.15%) and non-molar gestational trophoblastic neoplasia 3 cases (3.66%). Mean age at diagnosis was 25.04 years (range 14-36 years). Median interval from remission to subsequent pregnancy was 36 months (range 3-132 months). There were 80 from 82 cases spontaneous pregnancy. Three patients (3.66 %) was pregnant before 1 year. For first subsequent pregnancy outcomes, 71 cases (86.66%) were term live birth, 3 cases (3.66%) were preterm birth and 8 cases (9.76%) were spontaneous abortion. There was no significant difference in pregnancy outcomes between patients who received chemotherapy and who did not receive chemotherapy treatment. Similarly, patients who received single agent chemotherapy and multi-agent chemotherapy had no significant difference in pregnancy outcomes.

Conclusion: Around 86% of subsequent pregnancy after GTD remission were term live birth. Subsequent pregnancy outcomes after GTD were not significantly different between patients with hydatidiform mole and gestational trophoblastic neoplasia.

Keywords: gestational trophoblastic disease, molar pregnancy, subsequent pregnancy, gestational trophoblastic neoplasia

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ผลของการตั้งครรภ์ในผู้ป่วยที่เคยตั้งครรภ์ไข่ปลาอุกหรือมะเร็งเนื้อรกที่รักษาในโรงพยาบาลจุฬาลงกรณ์

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการตั้งครรภ์ในผู้ป่วยภายหลังการรักษาครรภ์ไข่ปลาอุก หรือมะเร็งเนื้อรกในโรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลัง ตั้งแต่ปีพ.ศ. 2544-2558 โดยเก็บข้อมูลในผู้ป่วยที่ได้รับการวินิจฉัยเป็นครรภ์ไข่ปลาอุกหรือมะเร็งเนื้อรก ซึ่งเป็นกลุ่มโรค Gestational Trophoblastic Disease ในโรงพยาบาลจุฬาลงกรณ์ ข้อมูลรวบรวมมาจากบันทึกในเวชระเบียนและการโทรศัพท์สัมภาษณ์ผู้ป่วย โดยรวบรวมข้อมูลทางคลินิกและผลของการตั้งครรภ์หลังการรักษาโรค*

ผลการวิจัย: *ในช่วงเวลาที่ทำการศึกษา มีผู้ป่วยในโรคนี้ 147 ราย และมีการตั้งครรภ์ 82 ราย ผู้ป่วย 40 ราย (ร้อยละ 48.78) ได้รับการวินิจฉัยเป็น complete hydatidiform mole 11 ราย (ร้อยละ 13.41) ได้รับการวินิจฉัยเป็น partial hydatidiform mole 28 ราย (ร้อยละ 34.15) ได้รับการวินิจฉัยเป็นมะเร็งเนื้อรกที่เกิดตามหลังครรภ์ไข่ปลาอุก และ 3 ราย (ร้อยละ 3.66) ได้รับการวินิจฉัยเป็นมะเร็งเนื้อรกที่ไม่ได้เกิดตามหลังครรภ์ไข่ปลาอุก อายุเฉลี่ยของผู้ป่วยคือ 25.04 ปี ระยะเวลาตั้งแต่หายจากโรคจนตั้งครรภ์มีค่ามัธยฐานที่ 36 เดือน ผู้ป่วย 80 ราย สามารถตั้งครรภ์ได้เอง แต่พบผู้ป่วย 3 รายที่ตั้งครรภ์ก่อน 1 ปีนับจากระยะเวลาหายจากโรค ผลของการตั้งครรภ์พบว่า 71 ราย (ร้อยละ 86.66) คลอดครบกำหนด มี 3 ราย (ร้อยละ 3.66) คลอดก่อนกำหนด และ 8 ราย (ร้อยละ 9.76) แท้งบุตรไม่พบความแตกต่างในผลของการตั้งครรภ์อย่างมีนัยสำคัญระหว่างกลุ่มที่เป็นครรภ์ไข่ปลาอุก และกลุ่มที่เป็นมะเร็งที่ได้เคมีบำบัด เมื่อเทียบผลการตั้งครรภ์ในกลุ่มที่ได้เคมีบำบัดตัวเดียวกับกลุ่มที่ได้หลายตัวก็ไม่พบความแตกต่างเช่นกัน*

สรุป: *ผู้ป่วย Gestational Trophoblastic Disease ที่ตั้งครรภ์หลังการรักษา พบว่าร้อยละ 86 เป็นการคลอดครบกำหนด ไม่พบความแตกต่างในผลของการตั้งครรภ์อย่างมีนัยสำคัญระหว่างกลุ่มที่เป็นครรภ์ไข่ปลาอุกและกลุ่มที่เป็นมะเร็งที่ได้เคมีบำบัด*

คำสำคัญ: *ครรภ์ไข่ปลาอุก, การตั้งครรภ์ภายหลัง, มะเร็งเนื้อรก*

Introduction

Gestational trophoblastic disease (GTD) is the spectrum of disease caused from abnormal trophoblast cells or placenta which included benign disorder or hydatidiform moles to malignant conditions (Gestational trophoblastic neoplasia, GTN) such as choriocarcinoma, placental-site trophoblastic tumor and epithelioid trophoblastic tumor[1]. Incidence of GTD varies among countries, in Thailand prevalence was 1-2 per 1,000 pregnancies[2-4]. The incidence trends to be lower in western country[1]. Treatment of hydatidiform mole is primary evacuation of molar tissue and monitoring serum human chorionic gonadotropin (hCG) level. About 10-30% of hydatidiform mole patients develop postmolar GTN[1, 3]. Primary treatment of GTN is chemotherapy. So far, outcomes of GTN patients are excellent because most of them achieve remission[4].

Due to the pathogenesis of this condition results from abnormal fertilization, most of patients are in reproductive age[5]. Reproductive outcomes after treatment are critical issues for patients. There were several studies reported about pregnancy outcomes after hydatidiform mole and GTN[6-9]. However, there still lack of data from Thailand. Since the pathogenesis of GTD may relate to race and ethnicity. Therefore, the objectives of this study aimed to explore subsequent pregnancy outcomes after treatment in GTD patients and to compare outcomes of pregnancy between hydatidiform mole and GTN patients.

Materials and Methods

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. All patients whom diagnosed GTD between 2001 and 2015 were recruited. Hydatidiform mole was diagnosed by histologic specimens and GTN was diagnosed by the International Federation of Gynecology and Obstetrics (FIGO) criteria[10]. Patients who lost to follow-up or patients with medical conditions which contraindicated for pregnancy, or had no ability to pregnant (e.g. hysterectomy, tubal resection) were excluded. Data collection was retrieved from medical record and telephone interview. Clinical characteristics and data related to pregnancy outcomes in term of total pregnancy, total delivery, term live birth, preterm live birth, stillbirth, congenital anomaly, spontaneous abortion, therapeutic abortion, ectopic pregnancy, and repeat mole were collected. The pregnancy outcomes were collected only the first subsequent pregnancy after treatment of GTD. For single agent chemotherapy, we used either methotrexate or actinomycin D. For multi-agent chemotherapy, we used either EMACO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) or VAC regimen (vincristine, actinomycin D, cyclophosphamide). This study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The methods were performed in accordance with approved guidelines.

Sample size calculation was based upon the prevalence of normal pregnancy outcome after GTD from previous study[6]. SPSS version 22 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Mean, median, standard deviation (SD), percentage for nonparametric variables, student t-test for continuous variables, chi square for proportional data and analysis of variance (ANOVA) for many continuous variables. Statistically significant was considered if $p < 0.05$.

Results

From 1 January 2001 to 31 December 2015, there were 229 GTD patients registered at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. One hundred and twenty three patients were diagnosed as hydatidiform mole with remission, 70 patients were diagnosed as postmolar GTN and 36 patients diagnosed as non-molar GTN. Forty patients were excluded due to contraindicate or no ability to pregnant and 42 patients lost to follow-up. A total of 147 patients were recruited. The number of first pregnancy after remission of GTD were 82 patients. Among these patients, final diagnosis was complete hydatidiform mole 40 cases (48.78%), partial hydatidiform mole 11 cases (13.41%), postmolar GTN 28 cases (34.15%) and non-molar GTN 3 cases (3.66%).

Mean age at diagnosis was 25.04 years (range 14-36 years, SD 5.71). Median interval from remission

to first subsequent pregnancy was 36 months (range 3-132 months). There were 80 from 82 cases acquired spontaneous pregnancy. Three patients (3.66 %) were pregnant before 1 year, 2 of 3 cases were postmolar GTN with previous exposed to methotrexate. One of them had preterm birth, the other delivered term newborn. The third case was previously diagnosed of hydatidiform mole and achieved uneventful term delivery.

For pregnancy outcomes, 71 (86.66%) cases were term live birth, 3 (3.66%) and 8 (9.76%) cases were preterm birth and spontaneous abortion, respectively. There were no stillbirth, congenital anomalies, therapeutic abortion, ectopic pregnancy and repeat mole in this report. There were 48 (64.86%) cases delivered by normal labor and 26 (35.13%) cases by cesarean section. Average birth weight of newborn was 3,089.24 gram (SD 400.86).

When compare between hydatidiform mole and GTN patients. There was no significant difference in term of age, interval from remission to pregnancy, route of delivery and fetal outcomes (Table 1).

Table 1. Clinical characteristics and pregnancy outcomes compare between hydatidiform mole and GTN patients.

	Diagnosis		
	Hydatidiform mole (n = 51)	**GTN (n = 31)**	**p value**
Mean age at diagnosis (years, mean ± SD)	25.35 (5.87)	24.52 (5.48)	0.46
Median interval to pregnancy (months, range)	36 (10-132)	36 (3-132)	
Total number of pregnancy after remission			
1	35 (68.62%)	25 (80.64%)	0.55
2	14 (27.45%)	6 (19.36%)	
3	1 (1.96%)	0 (0%)	
4	1 (1.96%)	0 (0%)	
Method to pregnancy			
Natural	49 (96.08%)	31 (100%)	0.54
IUI	1 (1.96%)	0 (0%)	
IVF	1 (1.96%)	0 (0%)	
Delivered hospital			
KCMH	18 (35.29%)	9 (29.03%)	0.56
Other	33 (64.71%)	22 (70.96%)	
Route of delivery			
normal labor	30 (65.22%)	18 (64.28%)	0.94
LT C/S	16 (34.78%)	10 (35.72%)	
First subsequent pregnancy outcome			
term live	44 (86.27%)	27 (87.10%)	0.99
preterm live	2 (3.92%)	1 (3.22%)	
spontaneous abortion	5 (9.80%)	3 (9.68%)	
Sex of fetus			
male	27 (58.70%)	20 (71.43%)	0.27
female	19 (41.30%)	8 (28.57%)	
Average weight of fetus (gram, mean ± SD)	3,105.98 ± 327.30	3,061.75 ± 504.63	0.65

P value corresponds to independent t test and chi-square, GTN: Gestational trophoblastic neoplasia, SD: standard deviation, IUI: intrauterine inseminization, IVF: in vitro fertilization, KCMH: King Chulalongkorn Memorial Hospital, LT C/S: low transverse cesarean section

Similarly, patients who received single agent chemotherapy compared to multiple agent chemotherapy had no significant difference in age, duration to pregnancy and fetal outcomes (Table 2).

Table 2. Clinical characteristics and pregnancy outcomes compare between GTN patients who received single agent and multiple agent chemotherapy.

	Previous treatment		
	Single agent CMT (n = 24)	**Multi agent CMT (n = 7)**	**p value**
Mean age at diagnosis (years, mean ± SD)	24.12 (5.07)	26.17 (7.25)	0.12
Median interval to pregnancy (months, range)	36 (3-132)	30 (12-60)	
Total number of pregnancy after remission			
1	20 (83.33%)	5 (71.43%)	0.48
2	4 (16.67%)	2 (28.57%)	
Delivered hospital			
KCMH	9 (37.50%)	0 (0%)	0.05
Other	15 (62.50%)	7 (100%)	
Route of delivery			
normal labor	14 (63.64%)	4 (66.67%)	0.89
LT C/S	8 (36.36%)	2 (33.33%)	
First subsequent pregnancy outcome			
term live	21 (87.50%)	6 (85.71%)	0.78
preterm live	1 (4.17%)	0 (0%)	
spontaneous abortion	2 (8.33%)	1 (14.29%)	
Sex of fetus			
male	16 (72.73%)	4 (66.67%)	0.77
female	6 (27.37%)	2 (33.33%)	
Average weight of fetus (gram, mean ± SD)	3,124.73 ± 541.95	2,830.83 ± 245.16	0.21

P value corresponds to analysis of variance test and chi-square.
GTN: Gestational trophoblastic neoplasia, SD: standard deviation, CMT: chemotherapy,
KCMH: King Chulalongkorn Memorial Hospital,
LT C/S: low transverse cesarean section

Discussion

In general, GTD occurred in childbearing age. Hydatidiform mole can be treated by evacuation of molar tissue and GTN is mainly treated by chemotherapy. Therefore, treatment of GTD was primarily fertility preserved. As a result, most of GTD patients can pregnant after remission. For this reason, subsequent pregnancy outcomes in these patients are important. Joneborg U, et al,[11] conducted a population-based cohort study in Sweden showed that women with a history of hydatidiform mole had an increase risk in large for gestational age, preterm birth and stillbirth. In our data, the incidence of spontaneous abortion was approximately 10% in both hydatidiform mole and GTN patients which were comparable with spontaneous abortion in normal population[12, 13].

Vargas R, et al reported data about pregnancy outcome in 2,342 patients from New England Trophoblastic Disease Center after treatment of GTD and showed slightly increase stillbirth rate in GTD patients compared to normal population[6]. There was no stillbirth case in our finding, possibly due to small number of pregnant cases.

From our study, patients with previously diagnosed molar pregnancy or GTN had no significant difference in subsequent pregnancy outcomes with regard to term live birth, preterm birth and spontaneous abortion. Furthermore, interval to pregnancy, route of delivery, sex and weight of fetus were not different in both groups. This finding comparable to other studies in the world[7, 8, 14, 15].

Median interval from remission to first subsequent pregnancy was 36 months in this study. Compare to study from Kim JH, et al, more than half of patients became pregnant within 1 year after pregnancy was permitted[7]. This may explain from our follow-up protocol that strongly recommended for effective contraception at least 1 year after remission or complete chemotherapy. Furthermore, possible cause of long interval to subsequent pregnancy may be from patients' concern about following pregnancy after GTD. Leenharattanarak P, et al[16] reported quality of life after treatment in GTN patients were in mild impairment range. However, patients who desire fertility suffer lower quality of life in the emotional well-being domain. This data showed that fertility function was a major concern in this cancer survival patients. We found no statistical difference of interval to pregnancy between hydatidiform mole and GTN patients. Moreover, no difference in interval to pregnancy between patients who received single and multi-agent chemotherapy.

The results from this study can be applied to recommend patients who previously diagnosed GTD either hydatidiform mole or GTN that principally they can achieved reproductive outcome as normal population. However, limitations of this study were single institute and retrospective design that may result in small number of patients and some missing data.

Conclusion

In conclusion, around 86% of subsequent pregnancy after GTD remission were term live birth. Subsequent pregnancy outcomes after GTD were not significantly different between hydatidiform mole and GTN patients.

Potential conflicts of interest

The authors declare no conflict of interest.

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The Effectiveness of Sublingual Misoprostol in Reducing Operative Blood Loss during Total Abdominal Hysterectomy: A randomized controlled trial

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ABSTRACT

Objectives: To study the effectiveness and safety of preoperative sublingual misoprostol administration in reducing of operative blood loss during total abdominal hysterectomy (TAH).

Materials and Methods: Three hundred women with benign uterine diseases who were performed TAH at Khon Kaen Hospital from June 2017 to May 2018 were randomized into two groups: misoprostol group and placebo group. Intraoperative blood loss was analyzed.

Results: Baseline characteristics were similar between groups. There was no statistically significant difference in intraoperative blood loss between misoprostol and placebo group [228 ml (126-389) vs 240 ml (126-387), p = 0.943]. There was no significant difference in hemoglobin difference, blood transfusion and hospital stay between groups.

Conclusion: Misoprostol could not reduce intraoperative blood loss during total abdominal hysterectomy.

Keywords: benign uterine diseases, misoprostrol.

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ผลของยาไมโซพรอสตอลอมใต้ลิ้นในการลดปริมาณการเสียเลือดในระหว่างผ่าตัดตัดมดลูกทางหน้าท้อง: การทดลองแบบสุ่ม

ทิพย์สุคนธ์ หารินไสล, มนสิชา เมฆจรัสนภา, จรรยาภรณ์รัตนโกศล, มาลีชาติ ศรีพิพัฒนะกุล, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลและความปลอดภัยของยาไมโซพรอสตอลอมใต้ลิ้นในการลดปริมาณการเสียเลือดในระหว่างผ่าตัดมดลูกทางหน้าท้อง*

วัสดุและวิธีการ: *ผู้ป่วยหญิงที่ได้รับการวินิจฉัยเนื้องอกมดลูกทั้งหมด 300 ราย ที่เข้ารับการผ่าตัดมดลูกที่โรงพยาบาลขอนแก่น ในช่วงเดือนมิถุนายน 2560 ถึง พฤษภาคม 2561ได้รับการสุ่ม เป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยาไมโซพรอสตอลและกลุ่มที่ได้รับยาหลอก โดยดูปริมาณการเสียเลือดระหว่างผ่าตัดในกลุ่มที่ได้รับยาไมโซพรอสตอลเปรียบเทียบกับกลุ่มที่ได้รับยาหลอก*

ผลการวิจัย: *ลักษณะทางประชากรศาสตร์ไม่แตกต่างกันระหว่างสองกลุ่ม กลุ่มที่ได้รับยาไมโซพรอสตอลเสียเลือดระหว่างผ่าตัด 228 มล.(126-389) ส่วนกลุ่มที่ได้รับยาหลอกเสียเลือดระหว่างผ่าตัด 240 มล. (126-387) ซึ่งไม่มีความแตกต่างกันทางสถิติ เช่นเดียวกับความแตกต่างของความเข้มข้นของเลือดก่อนและหลังผ่าตัด การให้เลือด ระยะเวลาที่นอนโรงพยาบาล และภาวะแทรกซ้อนจากการให้ยา ที่ไม่มีความแตกต่างกันทางสถิติระหว่างสองกลุ่ม*

สรุป: *การให้ยาไมโซพรอสตอลไม่ช่วยลดปริมาณการเสียเลือดระหว่างผ่าตัดมดลูกทางหน้าท้อง*

คำสำคัญ: *เนื้องอกมดลูกชนิดไม่รุนแรง, ยาไมโซพรอสตอล*

Introduction

Total abdominal hysterectomy (TAH) is the most common operation performed by the gynecologists. There are many indications for hysterectomy. Myoma uteri continues to be the most common indication for hysterectomy which is indicated for 40% of all abdominal hysterectomies and the second most common indication is adenomyosis (12.8%)[1].

Intraoperative blood loss requiring blood transfusion is one of the most frequently complications of this procedure, occurring in 2-12% of cases[2]. Several methods for reducing blood loss during TAH such as injection of gonadotropin-releasing hormone (GnRH) agonist, uterine artery ligation, uterotonic agents such as misoprostol, oxytocin before operation were studied. However, there are many studies showed that GnRH agonist may effective in reducing blood loss during TAH but may cause significant side effects, high cost and can use only short period of time[3].

Misoprostol, a synthetic analog of prostaglandin E1 is economical and stable in room temperature. It can be administered orally, rectally or sublingually and has no serious side effect[4]. It can lessen blood loss during TAH by decreasing in uterine artery blood flow due to direct vasoconstriction in uterine arteries. Strong myometrial contractions lead to increase contraction of the vessels supplying blood to the myoma and may also contribute to a reduction in bleeding[5].

In this study, we used sublingual route because a pharmacokinetic study found that sublingual misoprostol has shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes, it can avoid the first-pass metabolism via the liver that found in oral route, it is more convenient than using via vaginal or rectal administration, and no need to repeat dose because the uterine contraction is sustained and will decrease activity after 3 hours of drug administration. Patient undergoing TAH require preoperative cleaning of vagina so administration via vaginal route may be interfered[4].

According to the previous studies, Biswas et al, showed that a single dose of misoprostol administered before TAH resulted in a significant reduction of intraoperative blood loss[5]. By contrast, a similarly designed study by Panichpongpan, et al and Chai, et al, showed no significant effectiveness in reducing intraoperative blood loss during TAH by misoprostol administration before an operation[6, 7]. Therefore, we conducted this study because the previous studies have shown varying results and its effectiveness is still unproven.

Materials and Methods

Women with diagnosed of myoma uteri or adenomyosis who were scheduled to perform TAH between June 2017 and May 2018 at Khon Kaen Hospital were recruited, Written informed consent was obtained from each eligible participant. The study was approved by Khon Kaen Hospital Institute Review Board in Human Research and the randomization was generated by computer using block of four.

The participants were randomly allocated into two groups, study and control group. Study group received two tablets of 200 microgram misoprostol (Cytotec®), sublingually 30 minutes before the operation. Control group received two placebo tablets with identical in appearance to misoprostol. The drug was administered by unaware nurse at gynecologic ward. The randomization list was kept in a sealed opaque envelope.

Contraindications of misoprostol administration including mitral stenosis, glaucoma, sickle cell anemia, diastolic blood pressure over 100 mmHg, severe asthma, known allergy to prostaglandin, known case of coagulopathy, previous pelvic surgery, women who had pre-operative mifepristone or GnRH treatment, preoperative diagnosis of gynecologic cancer, emergency procedure and mental impairment or incompetent in giving consent were excluded.

We recorded blood pressure, pulse rate and body temperature at the time of admission and during 24 hours after administration of the drug. TAH with or without adnexal surgery was performed in the usual manner by the gynecological staff and residents.

Intraoperative blood loss was measured by adding blood volume in suction bottles to the difference in weight between the dry and wet swabs and gauzes before and after operation (1 gm is equivalent to 1 ml)[6] that measured by standard scales. The operative time from skin incision to close was recorded. Side effects of drug such as fever, chill, nausea/vomiting, diarrhea and headache were evaluated at 6 hours after the operation. Any intraoperative and postoperative transfusion were recorded. Hemoglobin level was determined by preoperative evaluation and 24 hours after the surgery. Postoperative diagnosis was confirmed by pathological report.

The sample size calculation was based on the data from Biswas, et al with 90% power at the 5% level of significance. The sample size in each group was 145 cases.

Differences in continuous variables were analyzed with student t-test or non-parametric test due to characteristics of data distribution and were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were analyzed by chi-square or fisher's exact test and were presented as number and percentage.

Results

There were 370 women who had been diagnosed of symptomatic myoma uteri or adenomyosis and underwent TAH with or without adnexal surgery. Sixty one women did not meet the criteria and nine rejected to participate in the study. Therefore, 300 women were recruited into the study, 150 in each group. Intraoperative finding found that there were three women who were diagnosed as ovarian tumor, 1 pelvic mass, 2 uterine cancer, 1 colon cancer, 1 endometrial polyp and 2 myomectomy, and five in each group. These women were withdrawn from the study (Fig. 1).

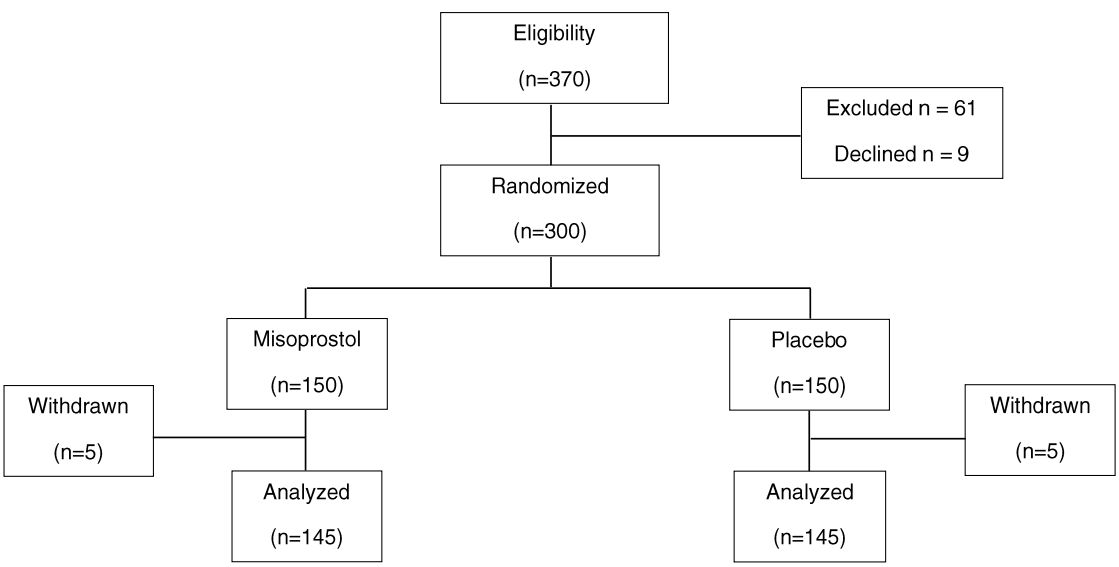

Fig. 1. Study flow.

Both groups had similar baseline characteristics such as age, body mass index (BMI), uterine weight, pre-operative hemoglobin (Hb), operation time, diagnosis and surgeon (Table 1). There was no significant difference of intraoperative blood loss between misoprostol and placebo group [228 ml (126-389) versus 240 ml (126-387)]. Similarity, the median of Hb difference, blood transfusion and length of hospital stay in both groups had no significant difference and serious

adverse effects were not found in both groups (Table 2).

Table 1. Demographic characteristics.

Characteristics	Misoprostol (n=145)	Placebo (n=145)	p value
Age (years)	46.2±5.2	45.5±5.2	0.203
BMI (kg/m^2)	25.3±4.3	24.9±4.3	0.338
Uterine weight (gm)	609±417.9	564.5±380.3	0.515
Preoperative Hb level (gm/dl)	11.5±1.7	11.3±1.6	0.579
Operative time (min)	90±25	91.8±29.2	0.607
Diagnosis			0.479
Myoma uteri	82 (56.55)	76 (52.41)	
Adenomyosis	63 (43.45)	69 (47.59)	
Surgeon			1.000
Staff	136 (93.79)	136 (93.79)	
Resident	9 (6.21)	9 (6.21)	

Data are presented as mean ± SD or n (%)
BMI: body mass index, Hb: hemoglobin

Table 2. Outcome measures.

Characteristics	Misoprostol (n=145)	Placebo (n=145)	p value
Intraoperative blood loss (ml)	228 (126-389)	240 (126-387)	0.943
Difference Hb (gm/dl)	1.1 (0.5-1.8)	1.2 (0.6-1.8)	0.203
Blood transfusion (unit)	5 (3.45)	5 (3.45)	1.000
Length of hospital stay (day)	4	4	0.391
Side effect			
Fever	52 (35.86)	43 (29.66)	0.260
Chill	10 (6.90)	7 (4.83)	0.309
Nausia and vomiting	49 (33.79)	47 (32.41)	0.803
Headace	6 (4.41)	6 (4.41)	1.000

Data are presented as median (IQR) or n (%)
Hb: hemoglobin

Discussion

This randomized controlled trial investigated the effect of effectiveness of preoperative sublingual misoprostol administration in reducing operative blood loss during total abdominal hysterectomy and safety. We found that misoprostol could not reduce intraoperative blood loss when compared to placebo.

The present study confirmed the similar results

of Panichpongpan, et al and Chai, et al revealed that using misoprostol 400 microgram did not reduce intraoperative blood loss. But with larger sample size, intraoperative blood loss was not significant different from those who received placebo. The possible reasons might be the different in degree of pelvic adhesion such as endometriosis was accidentally found during operation which was not excluded. Women with pelvic adhesion took risk of adjacent organs injury e.g. bowel, colon, ureter, bladder, etc. The variety of operative techniques of the surgeons were also one of all causes. Misoprostol induced uterine contraction resulting to reduce uterine blood flow only. But after the uterus was removed, the bleeding from other sources such as vaginal stump, the pedicles of cardinal ligaments could also cause additional bleeding.

By contrast, Biswas, et al reported that using misoprostol 400 microgram could significantly decrease evidence of intraoperative blood loss in myoma uteri patients who received TAH with or without BSO. However, intraoperative blood loss in misoprostol group was borderline lower than placebo group ($p = 0.049$).

There was no significant difference in serious side effects between misoprostal and placebo group. However, one of each group had fever which might be a reactionary fever after the operation (35.86% and 29.66% in misoprostol and placebo group, respectively). Other complications were nausea and vomiting from opioid effect (33.79% and 32.41% in misoprostol and placebo group, respectively).

The strengths of this study were a randomized double blinded, placebo controlled trial and measurement blood loss.

Limitations of this study were we studied only in elective cases as well as only in benign uterine diseases. Therefore, for further research, the study in difference population such as in gynecologic cancer patient or in case of emergency surgery should be considered.

Conclusion

Sublingual misoprostol 400 microgram before performing TAH with or without BSO in symptomatic myoma uteri or adenomyosis patients could not reduce intraoperative blood loss when compared to placebo.

Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

The Swede Score Colposcopic Evaluation in Prediction of High-Grade Lesions in Human Immunodeficiency Virus-Infected Patients with Abnormal Cervical Cytology

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ABSTRACT

Objectives: To evaluate the performance of the Swede score colposcopic scoring system at the different cut-off scores to predict high-grade lesions (HGL) in human immunodeficiency virus (HIV)-infected patient with abnormal cervical cytology.

Materials and Methods: A total of 80 HIV-infected patients undergoing colposcopic evaluation at Chonburi hospital, Thailand, due to their abnormal cervical cytological screening results, were included. All participants were evaluated with colposcopy and the findings were scored according to the Swede score system. Colposcopic directed cervical biopsy was performed in all cases. Then the final pathological diagnosis was compared with the recorded score. The performances of the Swede score for the prediction of HGL was determined by estimating the sensitivity, specificity, positive and negative predictive values of each cut-off point of total Swede score.

Results: The prevalence of HGL was 23.8%. All cases of HGL had a Swede score of 4 or above; therefore, sensitivity and negative predictive value for HGL at the cut-off score of 4 was 100%, and 100%, respectively. The maximum positive predictive value was only 47.8% at the cut-off score of 7 with the specificity of 80.3%. The specificity values at the cut-off scores of 8, 9, 10 were 83.6%, 88.5%, and 95.1%, respectively.

Conclusion: Swede Score was a good colposcopic scoring system which could be used as a screening tool to accurately exclude HGL in HIV-infected patients with abnormal cervical cytology when the total score was below 4. The specificity in HIV-infected patients was significantly lower than of that in non-HIV-infected patients; therefore, it required pathologic confirmation before treatment.

Keywords: swede score, colposcopy, high-grade lesions, HIV.

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การส่องกล้องปากมดลูกด้วยคอลโปสโคป โดยใช้ Swede Score พยากรณ์รอยโรคขั้นสูง ในผู้ป่วยเอชไอวีที่มีเซลล์เยื่อบุผิวปากมดลูกผิดปกติ

การัณย์ วีระพงศ์เศรษฐ์, สิทธิโชค มหาสุคนธชาติ

บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพในการพยากรณ์โรคขั้นสูงจากการส่องกล้องปากมดลูกด้วยคอลโปสโคป โดยใช้ Swede Score ในผู้ป่วยเอชไอวีที่มีเซลล์เยื่อบุผิวปากมดลูกผิดปกติ*

วัสดุและวิธีการ*: ผู้เข้าร่วมวิจัยเป็นผู้ป่วยเอชไอวีที่ได้รับการส่องกล้องปากมดลูกด้วยคอลโปสโคปที่โรงพยาบาลชลบุรี เนื่องจากมีเซลล์เยื่อบุผิวปากมดลูกผิดปกติ ทั้งหมดจำนวน 80 คน ทุกรายได้รับการส่องกล้องปากมดลูกด้วยคอลโปสโคป และประเมินรอยโรคโดยใช้ Swede Score ก่อนการตัดชิ้นเนื้อปากมดลูกส่งตรวจ หลังจากนั้นนำคะแนนที่ได้มาเปรียบเทียบกับผลวินิจฉัยของชิ้นเนื้อ เพื่อคำนวณหาความไว, ความจำเพาะ, ค่าทำนายผลบวก และค่าทำนายผลลบ ในการวินิจฉัยรอยโรคขั้นสูง ของแต่ละระดับคะแนนรวมของ Swede Score*

ผลการวิจัย*: ความชุกของรอยโรคขั้นสูงในการศึกษานี้เท่ากับร้อยละ 23.8 ผู้ป่วยทุกรายที่มีรอยโรคขั้นสูงมี Swede Score มากกว่าหรือเท่ากับ 4 ดังนั้น หากใช้จุดตัดคะแนนรวมในการวินิจฉัยเท่ากับ 4 ขึ้นไป จะมีค่าความไวและค่าทำนายผลลบร้อยละ 100 โดยที่จุดตัดคะแนนรวม 7 ขึ้นไป มีค่าทำนายผลบวกสูงที่สุดคือ ร้อยละ 47.8 และมีค่าความจำเพาะร้อยละ 80.3 ส่วนค่าความจำเพาะที่จุดตัดคะแนนรวม 8,9,10 คือ ร้อยละ 83.6, 88.5 และ 95.1 ตามลำดับ*

สรุป*: Swede Score เป็นเครื่องมือที่ดีในการคัดกรองผู้ป่วยเอชไอวีที่มีเซลล์เยื่อบุผิวปากมดลูกผิดปกติ โดยหากมีคะแนนรวมน้อยกว่า 4 จะสามารถแยกรอยโรคขั้นสูงออกได้อย่างแม่นยำ แต่มีค่าความจำเพาะต่ำกว่าเมื่อเทียบกับการใช้ในผู้ที่ไม่ติดเชื้อเอชไอวี ดังนั้นผู้ป่วยควรได้รับการยืนยันการวินิจฉัยจากการตัดชิ้นเนื้อตรวจก่อนให้การรักษา*

คำสำคัญ*: คอลโปสโคป, รอยโรคขั้นสูง, ผู้ป่วยเอชไอวี, เกณฑ์ประเมินลักษณะปากมดลูก*

Introduction

Cervical cancer is the second most frequent cancer among women in Thailand. Approximately 8,200 Thai women are diagnosed with cervical cancer and 4,500 die from the cancer every year[1]. Cervical intraepithelial neoplasia (CIN) is precancerous changes of the cervix uteri before progression to invasive cervical cancer, which classified according to the severity as CIN1, CIN2, and CIN3. The cervical cancer prevention includes cervical cytological screening to early diagnose CIN. However, cervical cytology diagnosis of CIN requires pathological confirmation, which colposcopy with directed biopsy is the standard. The current recommendation of management is observation for CIN1 and treatment for CIN2 and CIN3[2].

Risks of colposcopy with cervical biopsy include pain, bleeding, infection, psychological impact, inadequate biopsy, time consumption and high costs to patients[2]. The accurate colposcopic impression to predict high-grade lesions (HGL) (at least CIN2 or invasive cancer) without biopsy will decrease the risk of biopsy and facilitate see-and-treat strategy. However, colposcopy is the diagnostic procedure which operator affects the accuracy[3]. Strander, et al proposed a new colposcopic scoring system, the Swede score (Table 1), to make colposcopic impression less subjective and provides higher accuracy for detection of HGL, which included 5 parameters: acetouptake, margins and surface, lesion size, iodine staining, and vessels. They reported a 100% sensitivity of HGL at cut-off score of 5 and more than 90% specificity at cut-off score of 8 or higher[4]. The previous studies by Bowring, et al., and Kärrberg, et al., were conducted using the Swede score. The study of Bowring, et al., aimed to validate the Swede score conducted in London showed that a cut-off score of 2 had a sensitivity of 100% and a cut-off score of 8 or higher had a specificity of more than 95% in detecting HGL[5]. Furthermore, the study conducted by Kärrberg, et al., which was investigated in pregnant women, showed 100% sensitivity of HGL at a cut-off score of 5 and 70% specificity of HGL at a cut-off score of 8[6].

Several studies have illustrated that a higher prevalence of abnormal cervical cytology and CIN occurred among human immunodeficiency virus (HIV)-infected women than that in non-HIV-infected women[7-10]. The prevalence of HGL in HIV-infected woman with abnormal cervical cytology is high as 25%[7]. Therefore, if the Swede score can be applied to predict HGL accurately in these patients, it will decrease a substantial number of unnecessary biopsies. However, HIV-infected patients are associated with higher prevalence of sexually transmitted infection, including cervicitis[11], which affects the colposcopic accuracy[12] and make colposcopic impression in this population more challenging. To date, there have been no studies conducted to validate the use of Swede score particularly in HIV-infected population. The aim of this study was to evaluate the performance of the Swede score at a different cut-off scores to predict HGL in HIV-infected patients.

Materials and Methods

The study was approved by the Ethics Committee for Human Research of Chonburi Hospital. This diagnostic study was performed at the colposcopy clinic, Department of Obstetrics and Gynecology, Chonburi Hospital between June 2017 and August 2018. The participants were HIV-infected women undergoing colposcopy due to their abnormal cervical cytological screening results. The inclusion criteria for this study were HIV-infected woman who had abnormal cervical cytology of at least atypical squamous cells of undetermined significance (ASC-US). The exclusion criteria were known gynecological malignancy, pregnancy, history of hysterectomy, and allergy to iodine. A sample size of at least 80 was required base on the area under the receiver operating characteristic (ROC) curve of 0.87 taken from the previous literatures[4] and the area under the ROC curve from alternative hypothesis of 0.60 for 95% confidence interval estimates with 80% power

of the test.

The baseline characteristics were collected including age, obstetric profile, menstrual status, hormonal contraception use, history of smoking, result of cervical cytological screening, anti-retroviral drug use, viral load, and CD4 counts. All women were evaluated with colposcopy, performed by an experienced gynecologic oncologist, using standard methods with application of acetic acid 5% and Lugol's solution (iodine 5% and potassium iodide 10%). The colposcopic findings were scored according to the Swede score system (Table 1). Then colposcopic directed cervical biopsy was done in all cases. Then the specimens were interpreted by pathologists, and the pathological diagnosis was compared to the recorded colposcopic score. Patients were treated according to their histopathological results using standard guideline.

The sensitivity, specificity, positive and negative predictive values for HGL were calculated for each cut-off points of total Swede score. Then ROC curve was created and area under the curve (AUC) was computed.

Results

A total of 80 HIV-infected women who had abnormal cervical cytology were included. Their baseline characteristics are shown in Table 2. Antiretroviral drugs were used in 98.8% (79/80) of patients and 78.8% (63/80) had undetectable viral load (< 20 copies/ml). 13.8% (11/80) of patients had unknown viral load and 7.5% (6/80) patients had a detectable viral load which were 40, 212, 370, 538, 8885, and 92149 copies/ml. Mean CD4 count was 424.53 cells/µl (95% CI 369.79 – 479.27). The presenting cervical cytology were ASC-US 20% (16/80), LSIL 53.8% (43/80), ASC-H 5% (4/80), HSIL 13.8% (11/80), atypical glandular cells 6.3% (5/80), and squamous cell carcinoma 1.3% (1/80). All the pathological samples obtained were no CIN 37.5% (30/80), CIN1 38.8% (31/80), CIN2 17.5% (14/80), CIN3 5% (4/80) and squamous cell carcinoma 1.3% (1/80). Prevalence of HGL in this study was 23.8% (19/80).

After comparing the pathological diagnosis to the recorded Swede score, the sensitivity, specificity, positive and negative predictive values for HGL at the different threshold scores were presented in Table 3. All cases of HGL had a Swede score of 4 or higher, therefore sensitivity and negative predictive value for HGL at the cut-off score of 4 was 100%, and 100%, respectively. There was only one case of squamous cell carcinoma, which had a total Swede score of 6. The highest positive predictive value was 47.8% at the cut-off score of 7 with the specificity of 80.3%. The specificity values at the cut-off scores of 8, 9, 10 were 83.6, 88.5, and 95.1%, respectively.

The ROC curve using Swede score for predicting HGL in HIV-infected patients with abnormal cervical cytology is demonstrated in Fig. 1, with an overall AUC of 0.797 (95% confidence interval 0.702 – 0.891).

Table 1. Swede Score Model[1].

Score	0	1	2
Acetouptake	0 or transparent	Shady, milk	Distinct, opaque white
Margins and surface	0 or diffuse	Sharp but irregular, jagged, 'geographical', satellites	Sharp and even, difference in surface level including 'cuffing'
Vessels	Fine, regular	Absent	Coarse or atypical vessels
Lesion size	< 5 mm	5-15 mm or 2 quadrants	> 15 mm or 3-4 quadrants or endocervically undefined
Iodine staining	Brown	Faintly or patchy yellow	Distinct yellow

Table 2. Baseline Characteristics.

Characteristics	N (%)
Mean age ± SD (years)	40.1 ± 8.89
Previous vaginal delivery	
Nulliparity	22 (27.5%)
1	28 (35%)
2	18 (22.5%)
3	8 (10%)
4	4 (5%)
Menstrual status	
Premenopause	67 (83.8%)
Postmenopause	13 (16.3%)
Contraception	
Combined oral contraceptive pill	4 (5%)
DMPA (Depomedroxyprogesterone acetate)	5 (6.3%)
Etonogestrel implant	2 (2.5%)
Condom	17 (21.3%)
Female sterilization	22 (27.5%)
None	30 (37.5%)
Smoking	12 (15%)
Anti-retroviral drugs use	79 (98.8%)
Mean CD4 count ± SD (cells/μl)	424.53 ± 249.8
Viral load (copies/ml)	
Undetectable (< 20)	63 (78.8%)
Detectable	6 (7.5%)
No data	11 (13.8%)

Table 3. Performance of different Swede scores to detect high-grade lesions.

Cut-off score ≥	Number of women with score at cut-off level	Number of HGL with score at cut-off level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	20	0 (0.0%)	100	0	23.8	-
2	4	0 (0.0%)	100	32.8	31.7	100
3	7	0 (0.0%)	100	39.3	33.9	100
4	6	1 (16.7%)	100	50.8	38.8	100
5	8	3 (37.5%)	94.7	59.0	41.9	97.3

Table 3. Performance of different Swede scores to detect high-grade lesions. (Cont.)

Cut-off score ≥	Number of women with score at cut-off level	Number of HGL with score at cut-off level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
6	12	4 (33.3%)	78.9	67.2	42.9	91.1
7	5	3 (60.0%)	57.9	80.3	47.8	86.0
8	6	3 (50.0%)	42.1	83.6	44.4	82.3
9	7	3 (42.9%)	26.3	88.5	41.7	79.4
10	5	2 (40.0%)	10.5	95.1	40.0	77.3

HGL: High-grade lesion, PPV: Positive predictive value, NPV: Negative predictive value

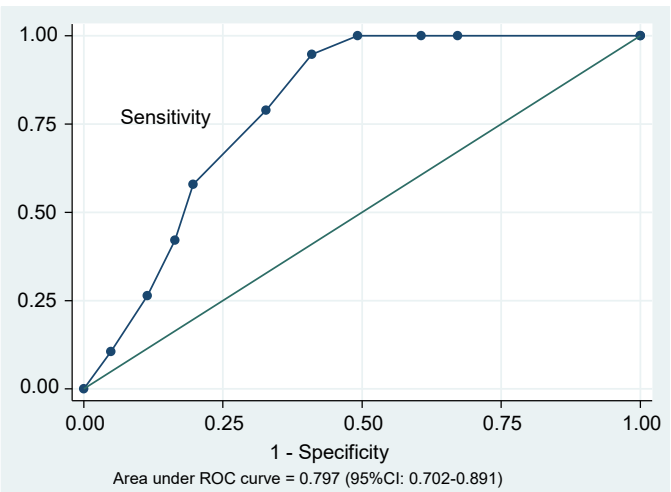

Fig. 1. Receiver operating characteristic (ROC) curve

Discussion

This is the first study to validate the performance of the Swede score for prediction of HGL in particular HIV-infected patients. Although almost all patients used antiretroviral drugs and had a low viral load, they had a high prevalence of HGL (23.8%), which was consistent with the previous study (25%)[7].

Low Swede scores in this study were well-correlated with low-grade lesions. None of the patient with HGL had a total Swede score less than 4. Moreover, at the score 4, there was only one case that had HGL. Therefore, if the colposcopic score is less than 4, it can safely exclude HGL and omit a cervical biopsy, which decrease the need of biopsies in 38.8% (31/80) of cases. When compared to the previous studies, the study in non-pregnant Swedish conducted by Strander, et al and the study in pregnant women conducted by Karrberg, et al, they used a cut-off score of 5 to identify HGL with 100% sensitivity[4,6]. The lower cut-off score found in this study may not be related to the HIV infection status, since there was only one case of HGL that had a total score of 4 and the another previous study, which performed in London by Bowring, et al, differently suggested a cut-off score of 2 even in

the general population[5]. However, further studies of using Swede score in HIV-infected population should be conducted to confirm this finding.

In the present study, high Swede scores were not highly specific with HGL. A cut-off score of 8 had a specificity of 83.6% for HGL, which was lower than the previous studies that had a specificity of 90% and 95%[4,5]. However, a lower specificity (70%) was founded in the study of pregnant women[6]. The maximum positive predictive value was only 47.8% at the cut-off score of 7 in this study. Even in the higher cut-off scores, there were no gain in positive predictive value. The rationale behind the low specificity may be from the high rate of false-positive assessment of colposcopic impression results associated with cervicitis that are frequently found in HIV-infected patients[11,12]. Because of the low positive predictive values in any cut-off scores in this study, it does not support the see-and-treat strategy without biopsy in this population.

All of the patients were examined by only one experienced gynecologic oncologists, which was the strength of this study. However, the limitations of this study included i) the relatively small sample size, ii) a colposcopist was not blinded for the presented cervical cytological results, and iii) the pathological reports were not from the same pathologist. Before the application of this scoring system in other populations, the accuracy should be validated first to obtain an appropriate cut-off score for that local population.

Conclusion

In conclusion, the Swede score was a good colposcopic scoring system with high sensitivity to detect HGL, which could be used as a screening tool in HIV-infected patients with abnormal cervical cytological screening results. The performance was similar to that of in non-HIV-infected patients, except for a significantly lower in specificity that required pathologic confirmation before treatment. With the appropriate selected cut-off score, this tool will decrease many unnecessary cervical biopsies and its side effects.

Potential conflicts of interest

The authors declare no conflict of interest.

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