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Reviewer acknowledgement 2023

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EDITORIAL

At the beginning of New Year 2023, it's time for beginning good things. May this year bring happiness, new inspirations and new success to all members of Royal Thai College of Obstetricians and Gynaecologists (RTCOG). Wish all of RTCOG members and families safe from COVID-19.

Editor in Chief and managing staff of the Thai Journal of Obstetrics and Gynecology (TJOG) already attended the meeting "System development and quality improvement of Thai journals in the Scopus database", which is a continuation of the project "Co-operation project TCI-TRF-Scopus" on Wednesday, December 7, 2022 at Anantara Riverside Bangkok Resort, Charoennakorn Road, Thonburi, Bangkok. The objectives of the meeting were to acknowledgment of the overview of the research project, demonstration of the use of the Thailand Editorial System (Thai ES), inviting experts from the reviewer pool, methods of transferring data from the Aries EM system to the Thai ES system, as well as analyzing the performance of all journals in the project and budget support for the 2nd year. Thai ES system has been used since January 2023. The quality of Thai Journal of Obstetrics and Gynaecology is continuously rising.

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

This first issue of TJOG 2023 contains many interesting articles. One special article is "Uterine Sarcomas: Pre- and Intra-operative Considerations". The contents include biomarkers, imaging, and intraoperative gross evaluation.

Happy New Year 2023

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

Thai Journal of Obstetrics and Gynaecology
January 2023, Vol. 31, No.1, pp. 2-10.

SPECIAL ARTICLE

Uterine Sarcomas: Pre- and Intra-operative Considerations

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ABSTRACT

Uterine leiomyomas are the most common indication for hysterectomy and myomectomy. Compared with the laparoscopic approach, the abdominal approach for hysterectomy is associated with a higher risk of a venous thromboembolic event, blood transfusion, prolonged hospital stays, wound pain, and infection. Unfortunately, some women with uterine mass undergoing surgery had unexpected uterine sarcomas. Spreading an unexpected uterine sarcoma during a hysterectomy or myomectomy can worsen the prognosis. Thus, a pre-operative diagnosis of uterine sarcomas is relatively challenging. Obstetrician-gynecologists should pre-operatively discuss the possibility of malignancy of the disease, risk, and benefit of the operative approach with the patient with a uterine mass. In this article, we reviewed the concerns of uterine sarcomas in patients with a uterine mass in terms of the disease incidence, pathological and clinical features, pre-operative evaluation tools such as biomarkers and imaging, intra-operative gross evaluation, and the roles of the intra-operative tissue containment system.

Keywords: hysterectomy, leiomyoma, myomectomy, power morcellation, uterine sarcoma.

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Introduction

Uterine leiomyoma is the most common benign tumor, affecting more than 50% of all reproductive women. Hysterectomy and myomectomy are used worldwide via open and minimally invasive surgery (MIS). For the past three decades, MIS has generally been accepted as having advantages over the conventional open approach of a lower complication rate, shorter hospital stay, less blood loss, and more rapid recovery[1, 2]. Morcellation is a surgical technique for reducing the size of the uterine or myomas into pieces or strips to facilitate tissue removal. A power morcellation of the unexpected uterine sarcomas significantly increases intraperitoneal spreading and is an independent poor prognostic factor for recurrence and death[3-5]. In response, the U.S. Food and Drug Administration (FDA) issued a safety communication in November 2014 warning "against the use of laparoscopic

power morcellators in the majority of women undergoing myomectomy or hysterectomy for the treatment of fibroids"[6]. After that, the rate of open surgery increased, and the rate of MIS decreased significantly from the study used by the American College of Surgeons National Surgical Quality Improvement Program database. The major and minor 30-day complication rates among women undergoing open hysterectomy for uterine fibroids increased significantly after the warning[7]. In February 2020, the FDA updated a safety communication "laparoscopic power morcellation for myomectomy or hysterectomy can be performed only with a tissue containment system". The additional recommendations included that clinicians should not use the laparoscopic power morcellations when the tissue is known or suspected malignancy, in patients who are postmenopausal or older than 50 years of age, or candidates for removal of tissue (en bloc) through the vagina or via a mini-laparotomy incision[8]. In December 2020, the FDA also published updated recommendations "the clinicians should be aware of the spread of benign uterine tissue when used an uncontained power morcellation, conducted a thorough pre-operative screening and shared decision-making, discuss the risks and benefits of all relevant treatment options with patients"[9].

However, a pre-operative diagnosis for uterine sarcomas is relatively problematic. This article aimed to review an estimated incidence, clinical and tumor characteristics, pre-operative evaluation methods such as biomarkers and imaging, and intra-operative concerns that may impact the risk of malignancy among women undergoing surgery for benign uterine leiomyomas.

Incidence

Uterine sarcomas are rare tumors that account for 3-7% of all uterine cancers[10]. Soft tissue sarcomas are uncommon tumors. About 40% of leiomyosarcomas among women were uterine in origin—an estimated incidence of 0.36 per 100,000 woman-years worldwide[11]. In 2021, the American College of Obstetricians and Gynecologists (ACOG) summarised that the risk of an unexpected leiomyosarcoma ranges from 1 in 498 to less than 1 in 10,000[2]. The Agency for Healthcare Research and Quality (AHRQ), including data from 136,195 women in 160 studies, reported that the risk of unexpected leiomyosarcoma might range from 1 in 770 surgeries to less than 1 in 10,000 surgeries for presumed symptomatic leiomyomas[12]. In Thailand, a retrospective review from two tertiary-care institutes reported that the incidence of uterine sarcomas was 0.37% in women with uterine mass undergoing surgery at Ramathibodi Hospital and 0.2% in women undergoing hysterectomy for presumed leiomyomas at Siriraj Hospital[13, 14].

Pathological features

The tumor stage is the most important prognostic factor. The International Federation of Gynecology and Obstetrics (FIGO) classification and staging system 2009 has specified uterine sarcomas reflecting their different biologic behavior; 1. leiomyosarcomas and endometrial stromal sarcomas; 2. adenosarcomas; and 3. carcinosarcomas (malignant mesodermal mixed tumors, MMMT) (Table 1)[15]. Carcinosarcomas account for 50% of the uterine sarcoma, followed by leiomyosarcomas (30%), endometrial stromal sarcomas (15%), and undifferentiated sarcomas (5%)[16]. However, carcinosarcoma was then reclassified as carcinomas of the endometrium due to biphasic neoplasm characteristics composed of malignant epithelial and mesenchymal elements. Moreover, the recent data confirm that the sarcomatous component is derived from carcinoma or a divergent stem cell differentiation[17].

Thus, leiomyosarcomas are the most common subtype of uterine sarcomas. It often presents with a huge mass or with leiomyomas. The cut surface is typically soft, bulging, fleshy, necrotic, and hemorrhagic, lacking the prominent whorled appearance of leiomyomas[16]. Surgeons may be concerned about leiomyosarcomas while opening gross specimens intra-operatively. The role of frozen section is unclear. Artifacts caused by the freeze-drying of tissue may cause alterations in cellular appearance which is a potential source of interpretational error in frozen section. Furthermore, the result from frozen section do not have immediate therapeutic consequences in many cases[18]. The histology in permanent section

shows the constellation of hypercellularity, severe nuclear atypia, and high mitotic rate generally exceeding 15 mitotic figures per 10 high-power fields (M.F./10 HPF)[16, 19]. They are very aggressive and have poor prognoses. In the early stage of tumors confined to the uterus, recurrence rates range from 53 to 71%[10]. First recurrences occur in the lungs in 40% of patients and the pelvis in only 13%[20].

Table 1. FIGO staging for uterine sarcomas (2009)[15].

Stage	Definition
(1) Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to the uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvis tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(2) Adenosarcomas	
I	Tumor limited to the uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half of myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvis tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to the pelvis and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
(3) Carcinosarcomas Carcinosarcomas should be staged as carcinomas of the endometrium	

[a] Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis associated with ovarian/pelvic endometriosis should be classified as independent primary tumors.

Clinical features

Many retrospective studies review clinical presentations and associated factors of uterine sarcomas. Leiomyosarcomas tend to occur in old age. The study from the Ottawa Hospital reported the mean age in women with sarcomas as 62.1 ± 10.1 years (mean ± S.D.)[21]. Postmenopausal status and representing symptoms such as abnormal uterine bleeding, postmenopausal bleeding, palpable mass, rapid growth mass, and single uterine mass are reported as independently associated with increased risk of uterine sarcoma[13, 14, 21-25]. A definition for rapid growth is still indescribable and relies on subjective clinical assessment[13, 21]. The higher uterine weight, more than 2,000 grams, was reported progressively increased the incidence by 15% (2 in 13 patients)[26].

Pre-operative evaluation

Occult uterine sarcomas are rare but aggressive. According to the non-specific clinical manifestations and even endometrial histological detection, additional modalities encourage distinguishing between benign and malignant as well as access degree, severity, or staging of diseases. With significantly advanced and raised management of leiomyomas, non-surgical treatment, or even MIS, the optimized pre-operative assessments, in terms of detected potential malignancy, are the most important. Here are the pre-operative investigation tools used in clinical decision-making nowadays.

- **Biomarkers**

No available serum marker could differentiate between leiomyomas and uterine sarcomas. Some studies showed that a decreased hemoglobin, neutrophilia, or increased neutrophil-to-lymphocyte ratio would likely lead to sarcomas[27, 28]. However, Carcinoma antigen-125 (CA 125) and lactate dehydrogenase (LDH) may play a role in the pre-operative diagnosis of uterine sarcomas and usually interpret as their results along with other diagnostic imaging[22]. The diagnostic accuracy of combined LDH and magnetic resonance imaging (MRI) was 100% compared with 93.1% in MRI alone and 95.2% in dynamic MRI[29].

- **Imaging**

- Ultrasonography and computerized tomography (C.T.) scan

The feasible ultrasonography or C.T. scan facilitates identifying discriminating features of a uterine mesenchymal subtype is not easy. Due to both benign and malignant tumors originating from the mesenchymal cell, the tumors and normal myometrial tissue are usually revealed in the same manner in both modalities. Moreover, detecting invasive or metastasis as malignant potency cannot be easier. Currently, ultrasonographic or C.T. scan diagnostic criteria are not proper and valuable[15, 30].

- MRI

MRI is the best-distinguished tool for the differential diagnosis of soft tissue tumors. Although it is considered limited accuracy, some interesting features or analytical techniques can help diagnose pre-operatively. In the common malignant type, leiomyosarcomas are presented with infiltrating myometrium and an ill-defined margin. Recently studies reviewed some essential checklists on MRI that are applicable (Table 2)[31]. These features of consideration are the tumor border, enhanced features in contrast media, and endometrial thickening.

Table 2. Summary of typical MRI features for uterine mesenchymal tumors[30].

	LMS	ESS	UES	AS	Leiomyoma	Endometrial carcinoma
Localization	Myometrium	Generally, endometrium; can be located in myometrium	Generally, endometrium; can be located in myometrium	Endometrium	Myometrium	Endometrium
Margin	Irregular and ill-defined	Irregular and nodular	Markedly irregular and nodular	Regular and well demarcated	Regular	Regular or irregular
T1 signal	Hypointense and heterogeneous (hemorrhage, calcification)	Hypointense	Heterogeneous	Predominantly, hypointense, heterogeneous	Low-to-intermediated signal; high signal foci-hemorrhagic degeneration	Hypo-to-isointense signal to normal endometrium
T2 signal	Intermediate-to-high signal	Hyperintense and heterogeneous; bands of a low signal corresponding to preserved myometrium	Heterogeneous (extensive hemorrhage and necrosis)	Multiseptated cystic appearance; can show multiple small hyperintense foci	Low signal (non-degenerated); high signal-cystic, myxoid degeneration	Hyperintense and heterogeneous relative to normal endometrium
Contrast enhancement	Early and heterogeneous	Moderate (more intense than endometrial carcinoma) and heterogeneous	Marked (generally more intense than usual myometrium) and heterogeneous	Marked (generally isointense compared to normal myometrium) and heterogeneous	Variable	Hypointense compared to normal myometrium
DWI	Generally, more restrictions (lower ADC value) than leiomyomas	High signal and low ADC	High signal and low ADC	Low signal (low-grade nature)	Variable; generally higher ADC values than LMS	High signal and low ADC

LMS: leiomyosarcoma, ESS: endometrial stromal sarcoma, UES: undifferentiated endometrial sarcoma, AS: adenosarcoma, DWI: diffusion-weighted imaging, ADC: apparent diffusion coefficient

Uterine sarcoma typically has some degree of invasion that is always seen as an irregular or ill-defined border on MRI. The incidences are 80.6-100% in uterine sarcomas compared with 3.8% in atypical leiomyomas[32]. In a previous study, this finding on MRI showed 78-84% sensitivity and 86-91% specificity of leiomyosarcoma[33].

Due to necrosis, the contrast media in the MRI study reveals a lack of contrast enhancement in this area, which is often central. Uterine sarcomas usually demonstrate heterogenous enhancement, a typical central unenhanced finding[31]. The 95-100% sensitivity and 68-73% specificity on contrast media MRI in pre-operatively detecting leiomyosarcoma were reported[33]. Although the area of hyalin, cystic or red cell degeneration found in typical leiomyomas are not specifically enhanced characteristics, together with assessed signal intensities (S.I.) in both standard T1 and T2 weight imaging (W.I.), have some unique S.I. characteristics[31]. Without a specific enhanced response in degenerating leiomyomas, degenerative leiomyomas may be partially separated. In addition, the unenhanced area of necrosis in sarcomas, mean, and ratio of contrast enhancement are increased earlier than in degenerating leiomyoma groups[32].

Heterogeneous hypo-intensity on T1W.I. is commonly manifested in leiomyosarcoma[34]. Although subacute hemorrhagic necrosis, presenting methemoglobin, demonstrates the area of hyperintensity T1W.I., only 1.3-18% of leiomyomas are found compared to 18-94% of sarcoma[31, 33, 35]. Furthermore, central or intralesional hemorrhage resulted in an increase of 7.38 times sarcomas risk over non-malignant lesions[36]. Without clinical red degeneration, e.g., painful or systemic inflammation such as fever, subacute tumor hemorrhage with a high-intensity area is highly suspicious of sarcomas. However, tumors with acute or chronic hemorrhage are seldom identified with this feature. On T2W.I., the uterine sarcoma frequency shows intermediate-to-high S.I., but intrauterine hemosiderin, caused by bleeding, results in a low T2 S.I. dark area[31, 34]. The overlapping high T2 S.I. in degenerative leiomyoma and leiomyosarcoma may confuse the interpretation, so the correlated analysis together with T1WI and characteristic of enhancement is valuable.

For the endometrial stromal sarcomas and adenosarcoma, uncommon subtypes of uterine sarcoma usually involve the endometrial part resulting in endometrial lining irregularity.

High diffusion-weighted imaging (DWI) S.I. and low apparent diffusion coefficient (ADC) values are highly suspected leiomyosarcoma[32, 37]. In the aforementioned red cell degeneration area, restricted diffusion of DWI area on T1 and T2 W.I. should be used for interpretation, especially in cellular leiomyoma and sarcoma. Table 3 summarizes the MRI features for the atypical leiomyoma[38].

Table 3. Summary of typical MRI features for atypical leiomyoma[37].

	Typical leiomyoma	Hyaline & cystic degeneration	Red degeneration	Lipo-leiomyoma	Cellular leiomyoma	Sarcoma
Border	Well defined	Well defined	Well defined	Well defined	Well defined	Lobulated or irregular
Enhancement	Heterogeneous	Heterogeneous with no enhancement in degeneration	Heterogeneous with no enhancement in degeneration	Heterogeneous	Homogeneous	Heterogeneous – with irregular outline/invasion
T1WI SI	Low	low	Hemorrhage high	Fat high with saturation on fat-saturated T1WI	Low	Low with high S.I. in areas of hemorrhage
T2WI SI	Low	High in cystic areas	Variable depending on the age of hemorrhage	Variable gave the fat-containing component	Intermediate	Intermediate and heterogeneous
Endometrial thickening	None	None	None	None	None	Direct involvement/irregular or thickened
Restricted diffusion	No	No	No	No	Yes	Yes

T1WI SI: T1 weighted imaging signal, T2WI SI: T2 weighted imaging signal

Intra-operative evaluation

Histopathological findings in each specific type of benign and malignant mesenchymal uterine tumors can be partially distinct from gross descriptions. In the group of non-malignant tumors, leiomyomas are subdivided into lipoleiomyoma, apoplectic or hydropic leiomyoma, dissecting leiomyoma, cellular leiomyoma, myxoid leiomyoma, epithelioid leiomyoma, symplastic leiomyoma, leiomyomatosis, or Not Otherwise Specified (NOS)[39]. NOS, or typical leiomyoma, is the most common benign intra-operative uterine tumor, found with well-circumscribed, unencapsulated, bulging, firm, white, and whirling on the cut surface that is less likely to be malignant with these features[39, 40]. On the other hand, other gross appearances defined differently from typical leiomyoma are atypical leiomyomas. Atypical leiomyomas may have some gross features that mimic uterine sarcoma. Some typical leiomyomas with degeneration or infarction mimic gross malignant characteristics.

Degenerated leiomyomas typically are seen as hyalin, cystic, or red cell degeneration. Red degeneration is well-circumscribed, bulging, retained whirling, and softening beefy-red color. In contrast, leiomyoma with infarction is dull-white or dull-yellowish[39]. Other atypical leiomyomas such as lipoleiomyoma, apoplectic leiomyoma, or cellular leiomyoma are usually found and hard to distinguish from uterine sarcoma. The mixture of lipocytes in smooth muscle tumors with a variable of bright yellowish lipoleiomyoma or softened yellowish well-circumscribed cellular leiomyoma is frequently assumed to be malignant potential uterine tumors[40].

The roles of intra-operative tissue containment systems

Because of the unreliable pre-operative diagnosis methods and intra-operative gross pathological documentation of uterine sarcoma, additional intra-operative containment bag morcellation was recommended[2, 8]. The tissue containment systems were then developed. PneumoLiner, a tube-like plunger containment bag, was approved by U.S. FDA in 2016; however, it has not been proven to reduce the risk of cancer spreading during the power morcellation[41] (Fig. 1)[42]. Using only in pre-menopausal women undergoing myomectomy or hysterectomy for non-fibroid related indications with pre-operative risk stratification and appropriate evaluations should be considered[2, 41]. Other systems are also available, e.g., EcoSac 230, Steri-Drape Isolation bag, LapSac Surgical Tissue Pouch Cook Medical, Anchor TRS-200, or EndoCatch 15 mm[43]. However, the perforation or leakage of the bag is a rising concern. Alternative approaches to morcellation in the bag removing intact specimens through the vagina or proper abdominal incision may be reduced the risk of spreading or leakage[44].

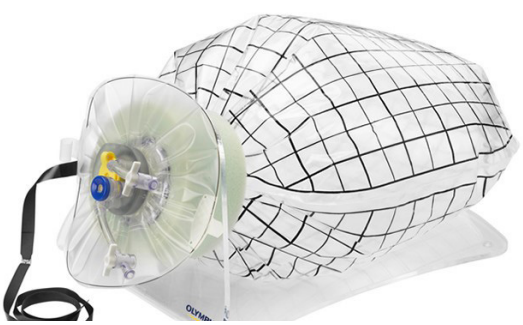

Fig. 1. PneumoLiner, The tissue containment systems[42].

Conclusion

Pre-operative diagnosis of uterine sarcomas in women with uterine mass undergoing hysterectomy and myomectomy is still problematic. Moreover, the intra-operative gross features of uterine sarcomas can mimic some types of leiomyomas. The surgeons, especially the gynecologic endoscopists, should discuss a higher procedural risk of hysterectomy or myomectomy with intra-abdominal tissue spillage and the risk of unexpected uterine sarcomas. The intra-operative containment systems play roles in reducing tumor spillage, although the perforation or leakage of the systems is worried. Further investigation is needed to improve the accuracy of pre-operative diagnostic methods and the security of intra-operative containment systems.

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OBSTETRICS

Cesarean Section Rate and Associated Risk Factors in Group 1 Robson Classification

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ABSTRACT

Objectives: To evaluate cesarean section (CS) rate among women in group 1 Robson classification, pregnancy outcomes and associated factors.

Materials and Methods: A total of 800 women classified in group 1 Robson classification were included. Data were extracted from medical records including maternal demographic data, obstetric characteristics, labor characteristics and management (cervical dilatation on admission, types of membranes rupture, cervical dilatation at artificial membranes rupture, labor augmentation, and use of analgesia), route of delivery, indications for CS, and pregnancy outcomes.

Results: Overall CS rate was 24.7%. Majority had cervical dilation at admission of < 5 cm (86%). Amniotomy was performed in 66.4% and, of which, 36.3% were performed when cervical dilatation of < 5 cm. Cephalopelvic disproportion (CPD) was the most common indication (74.7 %) followed by and non-reassuring fetal heart rate status (21.2%). Univariate analysis showed that maternal overweight and obesity, cervical dilatation of < 5 cm at admission, spontaneous rupture of the membranes, amniotomy at cervical dilatation of < 5 cm, gestational diabetes mellitus, and preeclampsia were significantly associated with CS. Logistic regression analysis revealed that significant independent factors for CS included overweight or obesity (adjusted odds ratio (OR) 1.58, 95% confidence interval (CI) 1.04-2.10, p = 0.033), amniotomy at cervical dilatation of < 5 cm and spontaneous rupture of membranes (adjusted OR 2.62, 95%CI 1.65-4.17, p < 0.001 and adjusted OR 2.87, 95%CI 1.82-4.53, p < 0.001 respectively).

Conclusion: CS rate among women in group 1 Robson classification was 24.7%. Maternal overweight and obesity, spontaneous rupture of membranes, amniotomy at cervical dilatation of < 5 cm, and preeclampsia were independent associated factors for CS.

Keywords: cesarean section, Robson classification, group 1, risk factors

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อัตราการผ่าตัดคลอดและปัจจัยเสี่ยงในสตรีตั้งครรภ์กลุ่ม 1 ตามการแบ่งแบบร็อบสัน (Robson Classification)

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราการผ่าตัดคลอด ผลลัพธ์ของการตั้งครรภ์ และปัจจัยเสี่ยงที่เกี่ยวข้องในสตรีตั้งครรภ์ที่จัดอยู่ในกลุ่ม 1 ตามการแบ่งแบบร็อบสัน (Robson classification)*

วัสดุและวิธีการ: *ทำการศึกษาในสตรีตั้งครรภ์ในกลุ่ม 1 ตามการแบ่งแบบร็อบสันทั้งหมด 800 ราย ทำการสืบค้นข้อมูลจากเวชระเบียน ประกอบด้วย ข้อมูลพื้นฐาน ข้อมูลทางสูติศาสตร์ ข้อมูลการคลอดและการดูแลรักษา (การเปิดของปากมดลูกขณะแรกรับ รูปแบบการแตกของถุงน้ำคร่ำ การเปิดของปากมดลูกขณะเจาะถุงน้ำคร่ำ การใช้ยากระตุ้นการหดรัดตัวของมดลูก และการให้ยาระงับปวด) ช่องทางการคลอด ข้อบ่งชี้การผ่าตัดคลอด และผลลัพธ์ของการตั้งครรภ์*

ผลการศึกษา: *อัตราการผ่าตัดคลอดเท่ากับร้อยละ 24.7 สตรีตั้งครรภ์ส่วนใหญ่มีการเปิดของปากมดลูก < 5 ซม. ขณะแรกรับ มีการเจาะถุงน้ำคร่ำร้อยละ 66.4 และร้อยละ 36.3 มีการเจาะถุงน้ำคร่ำขณะที่ปากมดลูกเปิด < 5 ซม. ภาวะช่องเชิงกรานไม่ได้สัดส่วนกับขนาดของศีรษะทารกพบเป็นข้อบ่งชี้หลักของการผ่าตัดคลอด (ร้อยละ 74.7) รองลงมาคือภาวะหัวใจทารกเต้นผิดปกติ (ร้อยละ 21.2) การวิเคราะห์แบบ univariate พบว่า มารดาน้ำหนักเกินและอ้วน การเปิดของปากมดลูก < 5 ซม. ขณะแรกรับ การแตกเองของถุงน้ำคร่ำ การเจาะถุงน้ำคร่ำขณะที่ปากมดลูกเปิด < 5 ซม. ภาวะเบาหวานขณะตั้งครรภ์ และภาวะครรภ์เป็นพิษ เป็นปัจจัยที่สัมพันธ์กับการผ่าตัดคลอดอย่างมีนัยสำคัญทางสถิติ การวิเคราะห์ถดถอยโลจิสติค พบว่าปัจจัยอิสระที่มีผลอย่างมีนัยสำคัญต่อการผ่าตัดคลอดคือ มารดาน้ำหนักเกินและอ้วน (adjusted odds ratio (OR) 1.58, 95% confidence interval (CI) 1.04-2.10, p = 0.033) การเจาะถุงน้ำคร่ำขณะที่ปากมดลูกเปิด < 5 ซม. และการแตกเองของถุงน้ำคร่ำ (adjusted OR 2.62, 95%CI 1.65-4.17, p < 0.001 และ adjusted OR 2.87, 95%CI 1.82-4.53, p < 0.001 ตามลำดับ)*

สรุป: *อัตราการผ่าตัดคลอดของสตรีตั้งครรภ์ในกลุ่ม 1 ตามการแบ่งแบบร็อบสันเท่ากับร้อยละ 24.7 มารดาน้ำหนักเกินและภาวะอ้วน การแตกเองของถุงน้ำคร่ำ การเจาะถุงน้ำคร่ำขณะที่ปากมดลูกเปิด < 5 ซม. และภาวะครรภ์เป็นพิษ เป็นปัจจัยอิสระที่สัมพันธ์กับการผ่าตัดคลอดบุตร*

คำสำคัญ: *การผ่าตัดคลอดบุตร, การแบ่งแบบร็อบสัน, กลุ่ม1, ปัจจัยเสี่ยง*

Introduction

Cesarean section (CS) is a life-saving intervention for women and newborns when complications occur, such as antepartum hemorrhage, fetal distress, abnormal fetal presentation, and hypertensive disease[1]. However, risk of various short- and long-term complications of current and future pregnancies are associated with the procedures, including uterine rupture, abnormal placentation, ectopic pregnancy, stillbirth, and preterm birth, and these risks increase in a dose–response manner[2-4]. According to the World Health Organization (WHO), appropriate CS rate should be between 10-15% and unnecessary procedures should be avoided because of potential risks of adverse outcomes without additional benefits to the mothers and their fetuses[1, 5].

Currently, there is a worldwide increase in CS rate in both developed and developing countries[6-8]. It is estimate that 29.7 million (21.1%) births occurred through CS in 2015, which was almost double the number of births by this method in 2000[6, 7]. Many previous reports showed that CS rate significantly increased in all the countries, including Thailand[2, 4, 8].

In classification of CS, the use of Robson classification system, which classify pregnant women into ten systematic groups (Table 1), is currently recommended by WHO and other international organizations[1, 5]. Previous systematic reviews identified this classification as the most appropriate system to fulfil current international and local needs[9, 10]. The use of a single CS classification will facilitate auditing, analyzing and comparing CS rates across different settings and help to create and implement effective strategies to optimize CS rates.

Increase in CS rate was also observed in Siriraj Hospital, which is a large university-based tertiary care hospital with over 6,000 deliveries each year. In 2017, Siriraj Hospital has adopted Robson classification system to identify pregnant women and evaluate CS rate. A recent report of data in 2017 showed that overall CS rate was 48.9%. The highest contribution of CS was in group 1 of Robson classification with CS rate of 37.1% and contributed to 23.2% of all CS[11]. Some interventions were then developed and implemented as an effort to reduce the high CS rate, especially among this specific group of women. Strategies to prevent primary CS was adopted from many recommendations[12-14]. This include changes in intrapartum care, such as active phase should be considered at cervical dilatation of 4-5 cm, abnormal cervical progression should not be limited to 1 cm/hour, early amniotomy should be avoided, etc.

Data on CS rate among women in group 1 of Robson classification is important that this group has the highest contribution to overall CS. In addition, women in group 1 Robson classification are considered low risk that the CS rate should not be too high compared to what is recommended. Understanding the rate and associated factors for CS, especially in this group of highest CS contribution, could help in planning appropriate strategies and interventions for reducing both group-specific and overall CS rate. Therefore, the primary objective of this study was to evaluate CS rate among women classified into group 1 of Robson classification. In addition, pregnancy outcomes and factors associated with CS were evaluated.

Materials and Methods

After study protocol was approved by Siriraj institutional review board, a cross-sectional study was conducted, including 800 pregnant women who were classified into group 1 of Robson classification, i.e., nulliparous with single cephalic pregnancy, ≥ 37 weeks gestation in spontaneous labor (Table 1) during September 2019 to March 2020. Cases with private care were excluded. A sample size was estimated from CS rate among women in group 1 Robson classification of 35%. At 95% significance level and 3.5% acceptable error, at least 786 women were needed, including 10% loss or incomplete data.

Table 1. Robson classification.

Group	Characteristics
Group 1	Nulliparous with single cephalic pregnancy, ≥ 37 weeks gestation in spontaneous labor
Group 2	Nulliparous with single cephalic pregnancy, ≥ 37 weeks gestation who either had labor induced (2a) or were delivered by caesarean section before labor (2b)
Group 3	Multiparous without a previous uterine scar, with single cephalic pregnancy, ≥ 37 weeks gestation in spontaneous labor
Group 4	Multiparous without a previous uterine scar, with single cephalic pregnancy, ≥ 37 weeks gestation who either had labor induced (4a) or were delivered by caesarean section before labor (4b)
Group 5	All multiparous with at least one previous uterine scar, with single cephalic pregnancy, ≥ 37 weeks gestation
Group 6	All nulliparous women with a single breech pregnancy
Group 7	All multiparous women with a single breech pregnancy, including women with previous uterine scars
Group 8	All women with multiple pregnancies, including women with previous uterine scars
Group 9	All women with a single pregnancy with a transverse or oblique lie, including women with previous uterine scars
Group 10	All women with a single cephalic pregnancy < 37 weeks gestation, including women with previous scars

Siriraj Hospital is the largest university-based tertiary care hospital with approximately 6,000 deliveries per year. Data on Robson classification were collected prospectively in a systematic manner since 2017. All necessary obstetric variables for Robson classification, including parity, number of fetuses, gestational age, previous CS, fetal lie and presentation, and route of delivery, were recorded using a specific form after delivery of each woman. Recorded data were later entered into a computer using a spreadsheet software and the data were checked and cleaned. Data analyses were performed and Robson classification was reported monthly.

In late 2019, changes in intrapartum care have been implemented according to various recommendations[12-14]. This included that active phase is considered at cervical dilatation of 4-5 cm, abnormal cervical progression should not be limited to 1 cm/hour, and early amniotomy should be avoided. This was in response to the high rate of CS observed during previous years and the audit of medical records on intrapartum care practice. The changes were clarified and distributed to all the residents and staff for cooperation. Although early amniotomy is advised to be avoided, individual judgment on amniotomy was under consideration of on duty residents under staff supervision, which was customized for each woman. Analgesics were also provided for women in active phase as necessary under consideration of caring physicians. Cephalopelvic disproportion (CPD) was diagnosed when labor fails to progress despite 4 hour of adequate uterine activity or at least 6 hours of oxytocin administration with inadequate uterine activity and no cervical change. Second opinion from on duty staff was mandatory for all decisions for CS.

Data were extracted from medical records including maternal demographic data, obstetric characteristics, labor characteristics and management, route of delivery, indications for CS, and pregnancy outcomes. Labor management included cervical dilatation on admission, types of membranes rupture, cervical dilatation at artificial membranes rupture, labor augmentation, and use of analgesia were also reviewed.

Continuous variables were reported as mean and standard deviation (SD), while categorical variables were reported as percentage. Pregnancy outcomes were compared between those with CS and vaginal deliveries using student t test and chi square test as appropriate. Risk of CS according to various characteristics were evaluated. Relative risks (RR) and 95% confidence intervals (CI) were estimated. Independent risk associated with CS were determined by logistic regression analysis. Adjusted odds ratio (OR) and 95%CI were estimated. A p value of < 0.05 was considered statistically significant.

Results

A total of 800 pregnant women in group 1 Robson

classification were reviewed and included. Baseline characteristics of the women are shown in Table 2. Mean maternal age was 27 years and mean gestational age was 38.6 weeks. Mean body mass index (BMI) was 21.8 kg/m^2 and 17.7% were overweight or obese. Gestational diabetes mellitus (GDM), chronic hypertension, and preeclampsia was found in 11.9%, 4.1%, and 3.8%, respectively.

Table 2. Baseline characteristics of pregnant women (n = 800).

Characteristics	n (%)
Mean age ± SD (years)	27.0 ± 6.2
Mean GA ± SD (weeks)	38.6 ± 1.0
Mean BMI ± SD (kg/m^2)	21.8 ± 4.4
BMI category	
Normal	490 (61.3)
Underweight	168 (21)
Overweight/obese	142 (17.7)
Complications	
GDM	95 (11.9)
Chronic hypertension	33 (4.1)
Preeclampsia	30 (3.8)

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

Labor and delivery characteristics of pregnant women are shown in Table 3. Majority had cervical dilation at admission of < 5 cm (86%). Amniotomy was performed in 66.4% and 36.3% were performed when cervical dilatation of < 5 cm. Labor was augmented in 64% and 48% received analgesia during labor. Overall CS rate in this study was 24.7 %. CPD was the most common indication (74.7 %) followed by and non-reassuring fetal heart rate (FHR) status (21.2%). Mean birth weight was 3,051.3 g and majority were appropriate for gestational age (AGA) (82.9%).

Table 3. Labor and delivery characteristics of pregnant women (n = 800).

Characteristics	n (%)
Cervical dilation at admission	
< 5 cm	688 (86)
≥ 5 cm	112 (14)
Rupture of membranes	
Spontaneous	269 (33.6)
Amniotomy at < 5 cm	290 (36.3)
Amniotomy at ≥ 5 cm	241 (30.1)
Augmentation of labor	512 (64)
Received analgesia	384 (48)
Route of delivery	
Vaginal delivery	602 (75.3)
Cesarean section	198 (24.7)
Indications of CS (n = 198)	
CPD	148 (74.7)
Non-reassuring FHR	42 (21.2)
Others	8 (4.1)

Table 3. Labor and delivery characteristics of pregnant women (n = 800). (Cont.)

Characteristics	n (%)
Birth weight for gestational age	
AGA	663 (82.9)
SGA	98 (12.3)
LGA	39 (4.8)
Macrosomia	7 (0.9)
Low birth weight	50 (6.3)
Apgar score 1 min < 7	24 (3)
Apgar score 5 min < 7	3 (0.4)
NICU admission	3 (0.4)

CS: cesarean section, CPD: cephalopelvic disproportion, FHR: fetal heart rate, SD: standard deviation, AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, NICU: neonatal intensive care unit

Comparisons of characteristics between those with vaginal delivery and CS were performed to evaluate possible associated factors for CS and the results are displayed in Table 4. Those with CS had significantly higher maternal age and BMI (p < 0.001). Risk of CS significantly increased among overweight or obese women (RR 1.5, 95%CI 1.1-1.9, p = 0.009). Cervical dilatation of < 5 cm at admission significantly increased the risk of CS (RR 2.1, 95%CI 1.3-3.5, p = 0.001). Spontaneous rupture of the membranes and amniotomy at cervical dilatation of < 5 cm also significantly increased the risk of CS (RR 2.2, 95%CI 1.5-3.2, p = 0.001 and RR 2.3, 95%CI 1.6-3.3, p < 0.001, respectively). GDM and preeclampsia also significantly increased the risk of CS (RR 1.5, 95%CI 1.1-2.0, p = 0.016 and RR 2.7, 95%CI 2.0-3.7, p < 0.001, respectively).

Table 4. Risk of CS according to various characteristics.

Characteristics	Vaginal delivery (n = 602)	CS (n = 198)	RR (95%CI)	p value
Mean age ± SD (years)	26.3 ± 5.9	28.9 ± 5.9		< 0.001
Mean BMI ± SD (kg/m^2)	21.4 ± 4.1	22.8 ± 4.9		< 0.001
BMI category				0.007
Normal	374 (76.3%)	116 (23.7%)	1.0	
Underweight	135 (80.4%)	33 (19.6%)	0.8 (0.6-1.2)	0.283
Overweight/obese	93 (67%)	49 (33%)	1.5 (1.1-1.9)	0.009
Cervical dilation at admission				0.001
≥ 5 cm	98 (87.5%)	14 (12.5%)	1.0	
< 5 cm	504 (73.3%)	184 (26.7%)	2.1 (1.3-3.5)	
Rupture of membranes				0.048
Amniotomy at ≥ 5 cm	209 (86.7%)	32 (13.3%)	1.0	
Amniotomy at < 5 cm	202 (69.7%)	88 (30.3%)	2.3 (1.6-3.3)	< 0.001
Spontaneous	191 (71%)	78 (29%)	2.2 (1.5-3.2)	< 0.001
GDM				0.016
No	540 (76.6%)	165 (23.4%)	1.0	
Yes	62 (65.3%)	33 (34.7%)	1.5 (1.1-2.0)	

Table 4. Risk of CS according to various characteristics. (Cont.)

Characteristics	Vaginal delivery (n = 602)	CS (n = 198)	RR (95%CI)	p value
Preeclampsia				<0.001
No	591 (76.8%)	179 (23.2%)	1.0	
Yes	11 (36.7%)	19 (63.3%)	2.7 (2.0-3.7)	
Chronic hypertension				0.631
No	576 (75.1%)	191 (24.9%)	1.0	
Yes	26 (78.8%)	7 (21.2%)	0.9 (0.4-1.7)	
Augmentation of labor				0.054
No	228 (79.2%)	60 (20.8%)	1.0	
Yes	374 (73%)	138 (27%)	1.3 (1.0-1.7)	
Received analgesia				0.738
No	311 (74.8%)	105 (25.2%)	1.0	
Yes	291 (75.8%)	93 (24.2%)	0.9 (0.7-1.2)	

CS: cesarean section, RR: risk ratio, CI: confidence interval, SD: standard deviation, BMI: body mass index, GDM: gestational diabetes mellitus

Comparison of pregnancy outcomes between women with vaginal delivery and cesarean section are shown in Table 5. Women with CS had significantly higher mean birth weight and more likely to have large-for-gestational-age (LGA) and macrosomia ($p < 0.001$). In addition, they were more likely to have infants with 5-minute Apgar score of < 7 ($p = 0.015$). Immediate postpartum hemorrhage was comparable between the 2 groups. No other serious adverse events were observed in both groups.

Table 5. Comparison of pregnancy outcomes between women with vaginal delivery and cesarean section.

Characteristics	Vaginal delivery (n = 602)	CS (n = 198)	p value
Mean birth weight ± SD (g)	2,999.8 ± 351.2	3,207.8 ± 436.1	< 0.001
Birth weight for gestational age			< 0.001
AGA	496 (82.4%)	167 (84.3%)	
SGA	86 (14.3%)	12 (6.1%)	
LGA	20 (3.3%)	19 (9.6%)	
Macrosomia	1 (0.2%)	6 (3%)	< 0.001
LBW	42 (7%)	8 (4%)	0.139
Immediate postpartum hemorrhage	45 (7.5%)	12 (6.1%)	0.502
Apgar score 1 min < 7	16 (2.7%)	8 (4%)	0.323
Apgar score 5 min < 7	0 (0%)	3 (1.5%)	0.015
NICU admission	1 (0.2%)	2 (1%)	0.153

CS: cesarean section, SD: standard deviation, AGA: appropriate for gestational age, SGA: small for gestational age, LGA: large for gestational age, LBW: low birth weight, NICU: neonatal intensive care unit

Logistic regression analysis was performed in order to determine independent risk for CS (Table 6). After adjusting for potential confounders, significant independent factors for CS included overweight or obese (adjusted OR 1.58, 95%CI 1.04-2.10, $p = 0.033$), amniotomy at cervical dilatation < 5cm and spontaneous rupture of membranes (adjusted OR 2.62, 95%CI 1.65-4.17, $p < 0.001$ and adjusted OR 2.87, 95%CI 1.82-4.53, $p < 0.001$, respectively)

Table 6. Logistic regression analysis to determine independent risk of cesarean section.

Risk factors	Adjusted OR	95%CI	p value
BMI category			
Normal	1.0		
Underweight	0.80	0.51-1.25	0.325
Overweight/obese	1.58	1.04-2.10	0.033
Rupture of membranes			
Amniotomy at ≥ 5 cm	1.0		
Amniotomy at < 5 cm	2.62	1.65-4.17	< 0.001
Spontaneous	2.87	1.82-4.53	< 0.001
Preeclampsia	5.31	2.42-11.65	< 0.001

Adjusted for age, cervical dilatation at admission, augmentation of labor, GDM, chronic hypertension
OR: odds ratio, CI: confidence interval, BMI: body mass index, GDM: gestational diabetes mellitus

Discussion

The study included 800 women who were classified in group 1 of Robson classification during September 2019 to March 2020. Overall CS rate was 24.7%. The CS rate was lower than a previous study from the same institution of 37.1%[11]. The lower CS rate among this group of women might possibly due to the changes in intrapartum care that were adopted from many recommendations[12-14], which included that active phase should be considered at cervical dilatation of 4-5 cm, abnormal cervical progression should not be limited to 1 cm/hour, early amniotomy should be avoided, etc. However, the rate was still higher than what was recommended by WHO[1], possibly due to the nature of the hospital which is a tertiary care institute. In terms of CS indications, majority of CS indication in this study was CPD which was similar to a previous report[15].

In this study, amniotomy was performed in 66.4% and 36.3% was done when cervical dilation was < 5 cm. The results also showed that risk of CS significantly increased when amniotomy was performed at cervical dilatation of < 5 cm compared to ≥ 5 cm. As recommended by World Health Organization (WHO), American College of Obstetricians and Gynecologists (ACOG), and The Society for Maternal-Fetal Medicine (SMFM), the use of amniotomy alone, and early amniotomy with early oxytocin augmentation for prevention of delay in labor is not recommended[13, 14, 16, 17]. The recommendation was based on that there was not enough evidence that early amniotomy could reduce the duration of first stage of labor, reduce CS and improve other clinical outcomes[13]. It is also possible that early amniotomy before active phase was reached could also increase the risk of other complications such as infection, especially as first stage would continue for a longer period of time than after active phase. Increased in CS rate was also observed in those with spontaneous membranes rupture as well. This could possibly be due to variations in labor management and differences in decision of CS. More detailed information and analysis are needed to elucidate the definite explanations.

As expected, maternal overweight and obesity were another significant associated factor for CS that was observed in this study. Similar findings have been reported from previous studies[18, 19]. A recent analysis of women in group 1 Robson classification from WHO global survey on maternal and perinatal health, 2004-2008, also showed significant association between maternal overweight and obesity and increased CS rate. (18) It is also suggested that there should be worldwide strategies and interventions to reduce overweight and obesity among women intending to become pregnant as well as maintaining appropriate gestational weight gain during pregnancy to reduce CS rate in the future[20].

The results also showed that preeclampsia was strongly increased the risk of CS. This was also similar to previous reports[21]. Being obstetrically high-risk is among significant factors associated with CS among women in group 1 Robson classification, as reported

by WHO[18]. The increased risk might be from the severity of the disease that could adversely affect fetal growth and well-being as well as possible deterioration with delayed delivery. Safe reduction of the rate of primary cesarean deliveries will require different approaches for each of these, as well as other indications.

Different approaches are required in order to safely reduce the CS rate among this group of women that should be customized for each setting with different contexts as well as individualized for each woman. In addition to some recommended clinical interventions, non-clinical interventions to reduce unnecessary CS are also recommended by WHO[22]. This should also be adopted into general practice as well.

Not surprisingly, rates of LGA and macrosomia were more common among those with CS as both conditions themselves increased the risk of the procedure. Other pregnancy outcomes were not clinically different between the 2 groups and no serious adverse event was observed. However, conclusion on safety issues of CS cannot be confirmed. Data on long-term complications as well as risks of adverse events in future pregnancies are not available from this study and needed to be evaluated in the future.

The strengths of this study may include that data on Robson classification is well-established and has been routinely and systematically record. Information of all included women were reviewed that misclassifications should be minimal. However, some limitations should be addressed. Detailed individual information on labor progression and management were incomplete and not readily available. Although a guideline for intrapartum management exists, there were some variations in actual labor management according to different attending staff and residents as well as variations in individual cases of pregnant women. Such information, therefore, could not be taken into account in the analysis. Although CS rate were reduced from previous report, data on CS-related complications were not included and compared. As data were from a single university-based tertiary care hospital in Thailand, further generalization of the results might be limited due to possible different population characteristics and clinical contexts.

Nonetheless, the results of this study revealed the nature of CS among women in group 1 Robson classification in terms of CS rate and possible associated factors. However, rooms for improvement should be further identified, possibly via regular audit cycles. This will help planning for appropriate strategies to further reduce unnecessary CS in the future. The study also showed that adjustment of intrapartum care protocol as recommended by many authorities could somehow help reducing the CS rate among women in group 1 Robson classification. However, the practice should be further customized to each setting with different contexts and resources. The use of Robson classification is encouraged in every setting to identify the problem and better plan for group-specific strategies to reduce unnecessary CS, customized for each setting. Future studies are still warranted in order to understand more about the increasing CS in other settings in Thailand, both for group-specific and overall CS rate to minimize unnecessary operations for better maternal and child health.

Conclusion

CS rate among women in group 1 Robson classification was 24.7%. Majority of indication was CPD. Maternal overweight and obesity, spontaneous rupture of membranes, amniotomy at cervical dilatation of < 5 cm, and preeclampsia were independent associated factors for CS.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Comparison of Clinical Characteristic and Survival Outcomes between Clear Cell and Non-Clear Cell Ovarian Cancer

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ABSTRACT

Objectives: To compare clinical characteristics and survival outcomes between women with clear cell carcinoma (CCC) and non-clear cell (NCC) epithelium ovarian cancer.

Materials and Methods: A retrospective cohort study was conducted on 220 Epithelial ovarian cancer (EOC) patients at Buddhachinaraj Hospital between January 1999 and May 2017. The patient data were retrieved from medical records. The patient characteristic, operative findings, histologic types, chemotherapy, time of recurrence, and follow-up time were analyzed. The medical records were comprehensively reviewed. The Kaplan-Meier method and Cox regression were employed in the survival analyses.

Results: A total of 220 EOC patients were eligible in the study, comprising 63 cases of CCC and 150 cases of NCC. Patients with CCC were more presented stage I and met optimal cytoreduction ($p < 0.005$). The progression-free survival (PFS) and overall survival (OS) were not statistically different between CCC and NCC when analyzed in all stages. However, PFS and OS were significantly different when classified EOC into three groups: NCC type I, type II EOC, and CCC. In stage I, CCC had better PFS ($p = 0.007$), but OS was no significant difference ($p = 0.279$). In stage II-IV, CCC had a trend toward poorer 5-year OS than type II EOC. The optimal surgery and complete course of platinum-based chemotherapy were associated with better survival outcomes in patients with epithelial ovarian cancer ($p < 0.001$).

Conclusion: The prevalence of CCC was 29.65% of EOC patients, and the majority found stage I. The PFS and OS were not statistically different between CCC and NCC.

Keywords: clear cell adenocarcinoma, epithelial ovarian cancer, survival analysis.

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การเปรียบเทียบลักษณะทางคลินิกและอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิด Clear Cell (CCC) และ Non-Clear Cell (NCC)

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บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบลักษณะทางคลินิกและอัตราการรอดชีวิตในผู้ป่วยมะเร็งรังไข่ชนิด Clear cell (CCC) และ Non-clear cell (NCC)*

วัสดุและวิธีการ: *การศึกษาย้อนหลังที่โรงพยาบาลพุทธชินราช พิษณุโลก ในผู้ป่วยที่ได้รับการวินิจฉัยและรักษาโรคมะเร็งรังไข่ชนิดเยื่อบุผิวตั้งแต่เดือนมกราคม 2542 ถึง ธันวาคม 2560 จำนวน 220 คน โดยเก็บข้อมูลพื้นฐานของผู้เข้าร่วมการวิจัยหรือข้อมูลเกี่ยวกับการดูแลรักษาของผู้ป่วยในด้านการผ่าตัด, ชนิดของมะเร็ง, การให้ยาเคมีบำบัด, ระยะเวลาการตรวจติดตามและระยะเวลาโรคกำเริบโดยการทบทวนแฟ้มเวชระเบียนผู้ป่วยแล้วนำข้อมูลที่ได้มาวิเคราะห์ทางสถิติและเปรียบเทียบอัตราการรอดชีวิต*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวเข้าเกณฑ์การศึกษาทั้งหมด 220 คนประกอบด้วยผู้ป่วยมะเร็งรังไข่ชนิด CCC 63 ราย และชนิด NCC 150 ราย กลุ่มผู้ป่วย CCC พบได้มากในระยะที่ 1 และได้รับการผ่าตัดแบบ optimal cytoreduction ($p < 0.005$) เมื่อวิเคราะห์กลุ่มผู้ป่วย CCC และ NCC ในทุกระยะของโรคไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระยะปลอดการลุกลามของโรค (PFS) และอัตราการรอดชีวิตทั้งหมด (OS) อย่างไรก็ตาม PFS และ OS มีความแตกต่างอย่างมีนัยสำคัญจากการจำแนกผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวออกเป็นสามกลุ่ม ได้แก่ NCC type I, Type II EOC และ CCC เมื่อเปรียบเทียบผู้ป่วยในระยะที่ 1 พบว่ากลุ่มผู้ป่วย CCC มี PFS ดีกว่า ($p = 0.007$) แต่ OS ไม่มีความแตกต่างอย่างมีนัยสำคัญ ($p = 0.279$) เมื่อเปรียบเทียบผู้ป่วยในระยะที่ 2-4 พบว่ากลุ่มผู้ป่วย CCC มีแนวโน้มอัตราการรอดชีวิตที่ระยะ 5 ปีน้อยกว่า Type II EOC ส่วนผู้ป่วยที่ได้รับการผ่าตัดแบบ optimal surgery และได้รับยาเคมีบำบัดสูตรแพลทตินั่มจนครบตามกำหนด พบว่าสัมพันธ์กับการรอดชีวิตมากขึ้นในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว ($p < 0.001$)*

สรุป: *ความชุกของผู้ป่วย CCC พบได้ถึงร้อยละ 29.65 ของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวและส่วนใหญ่มักพบในระยะที่ 1 อัตราการรอดชีวิตไม่มีความแตกต่างกันระหว่างกลุ่มผู้ป่วย CCC และ NCC อย่างไรก็ตามเมื่อจำแนกผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวเป็นสามกลุ่ม ได้แก่ NCC type I, Type II EOC และ CCC พบว่าอัตราการรอดชีวิตในกลุ่มผู้ป่วย NCC type I ดีที่สุด ส่วนอัตราการรอดชีวิตที่แย่ที่สุดพบในผู้ป่วยกลุ่ม Type II EOC ส่วนผู้ป่วยกลุ่ม CCC มีอัตราการอดชีวิตอยู่ระหว่างสองกลุ่ม*

คำสำคัญ: *มะเร็งรังไข่ชนิด clear cell, มะเร็งรังไข่ชนิดเยื่อบุผิว, การวิเคราะห์อัตราการรอดชีวิต*

Introduction

Ovarian cancer (OC) is a common gynecologic malignancy, resulting in death in women worldwide[1]. Epithelial ovarian cancer (EOC) accounts for more than 90% and holds different histology, biological behavior, and clinical characteristics. Serous carcinoma was the major subtype (75-80%). Clear cell carcinoma (CCC) was less common with high-grade nuclei mostly found, which made the CCC invasive in nature with significant clinical outcomes[2, 3].

The incidences of CCC vary across countries and ethnic groups. In western countries, North America, and Europe, the prevalence was 3-7%, while it was rising to 18% in Asia[4]. The Surveillance Epidemiology and End Results (SEER) showed a 5.6% prevalence of CCC in the female population of the USA and increased to 13.4% in the Asian women subgroup[5]. The prognostic of CCC is still debatable. Previously, CCC was defined as the high-risk histologic type for recurrence and lethal outcomes[6-8]. However, some reports showed that CCC had more favorable results in the early-stage[9, 10]. In the recent decade, integration of molecular genetics and histopathologic studies that lead to a better understanding of ovarian carcinogenesis. CCC was classified into the type I category, which is low-risk and has a better prognosis than the type II category[11]. However, CCC is still different from other non-clear cells (NCC) epithelium ovarian cancer by the age of onset, clinical course, and molecular genetics[2]. In the current surgical and chemotherapeutic guidelines, EOC can be managed according to disease stage and its histologic grading. If careful exploration of CCC and other NCC, it might be emerging new information for the clinical management of EOC. The purpose of this study was to compare clinical characteristics and survival outcomes between women with CCC and non-clear cell (NCC) epithelium ovarian cancer. The study also explored the survival outcome between NCC type I, type II EOC, and CCC.

The purpose of this study was to compare survival outcomes between women with CCC and NCC epithelium ovarian cancer. The secondary objectives were including 1) to compare clinical characteristic between women with CCC and NCC epithelium ovarian cancer, 2) to compare clinical characteristic between women with CCC, NCC type I, type II epithelium ovarian cancer, 3) to compare survival outcomes between women with CCC, NCC type I, type II epithelium ovarian cancer

Materials and Methods

The retrospective cohort study was conducted on one thousand patients who were diagnosed with epithelial ovarian cancer between January 1999 and May 2017 at Buddhachinaraj Phitsanulok Hospital, Thailand. The inclusion criteria were listed as follows: 1. patients received primary surgical treatment at the institution, 2. pathological confirmation of EOC, 3. complete follow-up information (complete medical record of clinical characteristic, surgery procedure, chemotherapy, date of loss to follow up/death)

The exclusion criteria were patients with histological diagnosis of mixed type OC or borderline and/or incomplete medical records or follow-up information (Fig. 1). The medical records were comprehensively reviewed. Baseline characteristics and clinical outcomes of all patients with EOC were collected for analysis. The variables used were age at diagnosis, risk of malignancy index (RMI) score [The RMI score is calculated based on the serum CA-125 value, menopausal status, ultrasound findings], stage at diagnosis [based on the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system], lymphovascular space invasion, peritoneal cytology status, type of primary surgery, presence of residual tumor when cytoreductive surgery was performed (categorized as no residual tumor, gross residual tumor < 1 cm, and residual tumor ≥ 1 cm), regimens and date of primary adjuvant chemotherapy completion, the date and site of the first progression or disease recurrence, and date and cause of death.

The standard guidelines for ovarian cancer treatment were complete staging surgery and cytoreductive surgery (CRS) with subsequent adjuvant chemotherapy in patients with high-risk early-stage (IB grade3, IC, II, clear cell) and advanced-stage III-IV disease, respectively. The majority of the patients received paclitaxel and carboplatin chemotherapy regimens from six to nine cycles. Gynaecological

oncologists operated to achieve optimal cytoreduction, which was defined as residual disease less than (or including) 1 cm after primary debulking. The postoperative follow-up consisted of a detailed medical history, physical examination, and serum CA-125 levels (categorized as abnormal if the level > 35 U/ml). Contrast-enhanced computed tomography of the abdomen and pelvis was performed when rising CA-125 or abnormal pelvic mass. The follow-up interval was varied about 3 to 4 months in the first 2 years, every 6 months in the 3rd to 5th year, and once a year thereafter. The platinum-sensitive disease group included patients who had relapsed more than six months after completion of the last platinum-based regimen. The overall survival (OS) was calculated from the date of their primary surgery to the date of death or last contact, and their progression-free survival (PFS) was determined from the date of their primary surgery to the date of first progression or recurrence. Type I EOC includes low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, while type II EOC comprises high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas.

The study was approved by the ethical committee of Buddhachinnaraj Hospital, IRB No. 085/61.

Statistical analysis

All descriptive data were shown in percentage, mean or median. Baseline characteristic data was performed with the Mann-Whitney U test (for continuous variables) and Pearson chi-square or Fisher exact tests for categorical variables. PFS and OS times were estimated using the Kaplan-Meier model. Predictors of survival outcomes were initially identified through stratified univariate analyses based on the log-rank test. Multivariate Cox proportional hazard regression models were used to analyze the independent predictors of survival. The histological diagnosis and variables with statistical significance in univariate analyses were entered into the models as covariates. Results were considered statistically significant if $p < 0.05$ (two-sided) and were expressed with their 95% confidence intervals. All statistical calculations were performed using the IBM SPSS statistical software (Version 22.0; IBM Inc., Armonk, NY, USA).

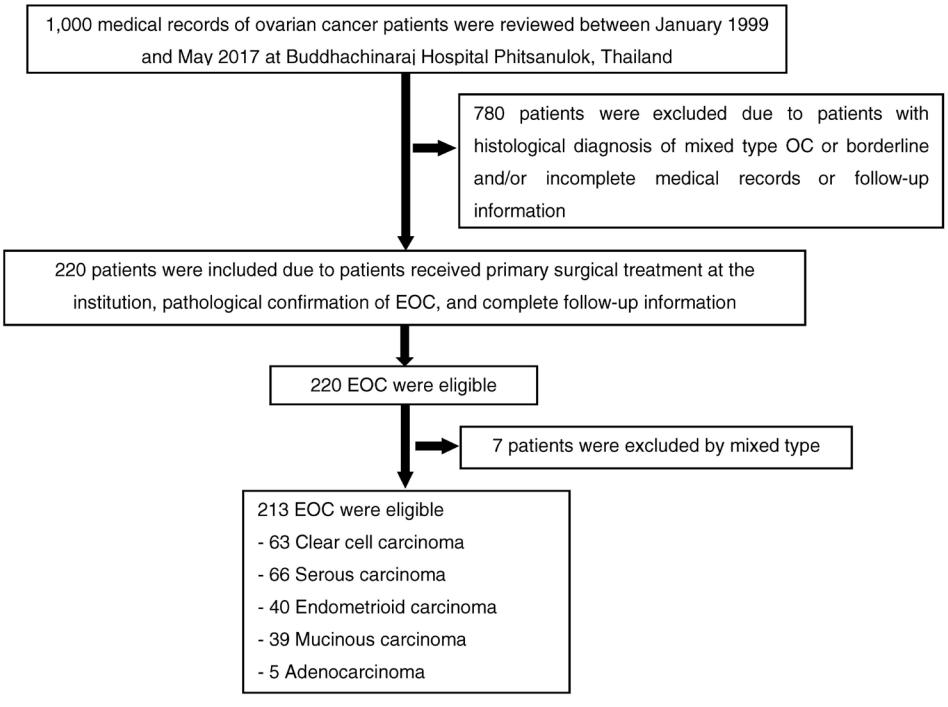

Fig. 1. The diagram of the enrollment patients.

OC: ovarian cancer, EOC: epithelial ovarian cancer

Results

A total of 220 EOC patients were eligible for the study. All 220 EOC were complete surgical staging surgery. However, seven were excluded from the analysis due to mixed histologic cell types. The pathologists had reviewed the pathological reports and slides. There were 63 CCC (29.6%), 66 serous cystadenocarcinoma (31%), 40 endometrioid carcinoma (18.8%), 39 mucinous carcinoma (18.3%) and 5 adenocarcinoma (2.3%); a total of 150 patients with NCC. Clinical characteristics and operative data of patients with CCC and NCC are shown in Table 1. Patients with CCC were more likely presented with pelvic mass compared with the patients with NCC (70.2% vs. 54.5%, p = 0.045). The patients in the CCC group had a lower median value of serum CA-125 and RMI score than the NCC group (198 vs. 496, p < 0.032 and 859 vs. 1,669, p < 0.043, respectively). Patients with CCC more often presented with FIGO stage I when compared with NCC (74.6% vs. 48.7%, p < 0.005). The percentage of optimal surgery in CCC was higher than NCC (87.3% vs. 72.7%, p < 0.021). The frequency of complete adjuvant chemotherapy ≥ six cycles in patients with CCC was also found to be higher (93.7% vs. 76.2%, p < 0.003). Coexisting with endometriosis was found to be more common in CCC than in NCC (41.3% vs. 9.5%, p < 0.001).

Table 1. Clinical characteristics and operative data of the patients.

Variables	CCC (n = 63)		NCC (n = 150)		p value
Age (years), mean (SD)	53.9	(9.0)	51.9	(11.9)	0.198
Oral contraception (%)	5/40	(12.5)	20/74	(27.0)	0.074
Menopausal status (%)					0.059
Premenopause	17/63	(27.0)	61/150	(40.7)	0.011
Postmenopause	46/63	(73.0)	89/150	(59.3)	0.013
Clinical presentation (%)					
Abdominal mass	40/57	(70.2)	72/132	(54.5)	0.045
Vaginal bleeding	3/57	(5.3)	7/57	(5.3)	0.999
Pelvic pain	25/57	(43.9)	51/132	(38.6)	0.502
Abdominal distention	22/57	(38.6)	62/132	(47.0)	0.288
Serum CA-125*, median (range)	198.0	(32.0 - 3,785.0)	496	(5.9 - 14,986.0)	0.032
RMI score*, median (range)	859.0	(0 - 34,065)	1,669	(0 - 134,874)	0.043
Optimal surgery (%)					0.021
No	8	(12.7)	41	(27.3)	
Yes	55	(87.3)	109	(72.7)	
Histopathology (%)					N/A
CCC	63	(100.0)	-		
MC	-		39	(26.0)	
EMC grade 1-2	-		25	(16.7)	
EMC grade 3	-		15	(10.0)	
LGSC	-		5	(3.3)	
HGSC	-		61	(40.7)	
Poorly differentiated denocarcinoma	-		5	(3.3)	
Associated endometriosis	26/63	(41.3)	14/148	(9.5)	< 0.001
FIGO 2014 staging (%)					0.005
I	47	(74.6)	73	(48.7)	
II	2	(3.2)	13	(8.7)	
III	13	(20.6)	1	(35.5)	
IV	1	(1.6)	63	(7.3)	
Lymph node metastasis (%)	8/59	(13.6)	14/115	(12.2)	0.795
Positive peritoneal cytology (%)	17/50	(34.0)	46/108	(42.6)	0.305
Adjuvant chemotherapy (%)	63/63	(100.00)	122/150	(81.3)	< 0.001
Adjuvant chemotherapy ≥ 6 cycles (%)	59/63	(93.7)	93/122	(76.2)	0.003

CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: Risk of malignancy index, MC: mucinous carcinoma, EMC: endometrioid carcinoma, LGSC: low-grade serous carcinoma, HGSC: high-grade serous carcinoma, FIGO: International Federation of Gynecology and Obstetrics
*Total no. of patients with serum CA-125 and RMI = 127, CCC = 41, NCC = 86

The median follow-up time was 49 months (range 1-232 months). The PFS and OS were not statistically significant differences between CCC and NCC when analyzed in all stages (Table 2 and Fig. 2).

Table 2. Survival outcomes compared CCC and NCC.

Variables	CCC (n = 63)	NCC (n = 150)	p value
Recurrence (%)	26 (41.3)	58 (38.7)	0.723
PFS analysis			0.820
Progression and recurrent rate/1,000 person-month	7.7	7.0	
3-year PFS (%)	68.0	62.4	
5-year PFS (%)	63.6	58.8	
Death (%)	17 (27.0)	46 (30.7)	0.591
OS analysis			0.848
Death rate/1,000 person-month	4.4	4.4	
3-year OS (%)	78.5	79.4	
5-year OS (%)	74.2	70.7	

CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, OS: overall survival, PFS: progression-free survival

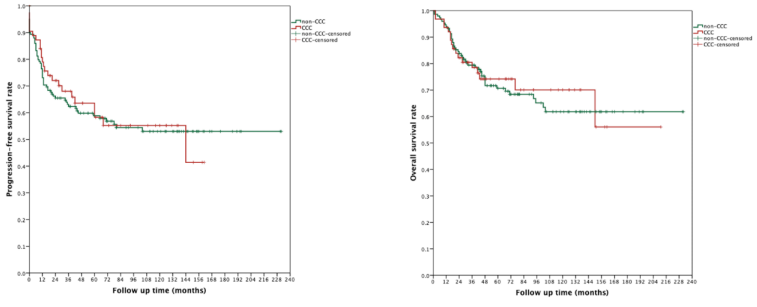

Fig. 2. The PFS and OS curves compared CCC and NCC groups.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

However, the PFS and OS analysis compared NCC type I, type II EOC, and CCC in all stages were significantly different (Table 3 and Fig. 3). The NCC type I EOC had the best prognosis. When comparing stage I, there was a significant difference in PFS but no significant difference in OS among EOC. However, PFS and OS of NCC type I, type II EOC, and CCC in stage II-IV were not significantly different with a trend toward a poorer outcome in CCC and type II EOC (Table 3, Fig. 4, 5).

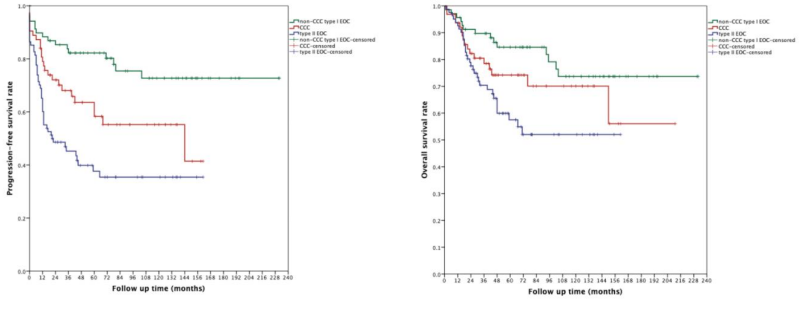

Fig. 3. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC in all stages.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

Table 3. Survival outcomes compared CCC, non-CCC type I, and type II EOC.

	Non-CCC type I EOC	CCC	Type II EOC	p value
All stage	(n = 69)	(n = 63)	(n = 81)	
PFS analysis				< 0.001
3-yr PFS (%)	82.2	68.0	45.2	
5-yr PFS (%)	82.2	63.6	37.6	
OS analysis				0.007
3-yr OS (%)	89.7	78.5	70.4	
5-yr OS (%)	84.6	74.2	57.5	
Stage I EOC	(n = 51)	(n = 47)	(n = 22)	
PFS analysis				0.007
3-yr PFS (%)	93.9	79.5	81.0	
5-yr PFS (%)	93.9	73.7	63.2	
OS analysis				0.279
3-yr OS (%)	98.0	91.4	90.9	
5-yr OS (%)	95.7	85.5	90.9	
Stage II-IV EOC	(n = 18)	(n = 16)	(n = 59)	
PFS analysis				0.475
3-yr PFS (%)	49.4	32.1	31.4	
5-yr PFS (%)	49.4	32.1	28.3	
OS analysis				0.629
3-yr OS (%)	66.2	40.4	62.5	
5-yr OS (%)	53.5	40.4	44.1	

CCC: clear cell carcinoma, EOC: epithelial ovarian cancer, OS: overall survival, PFS: progression-free survival

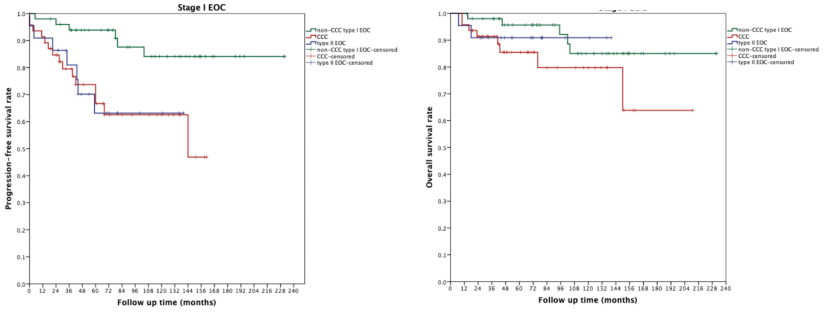

Fig. 4. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC stage I.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

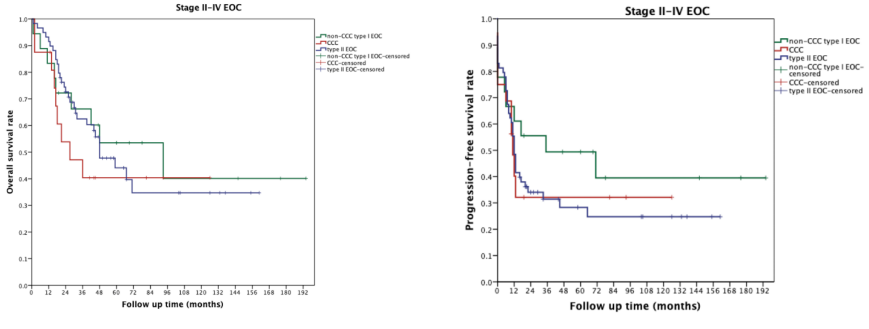

Fig. 5. The PFS and OS curves compared non-CCC type I, CCC, and type II EOC stage II-IV.

OS: overall survival, PFS: progression-free survival, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma

Univariate and multivariate survival analyses for PFS and OS are shown in Tables 4 and 5. The histological subtypes (NCC type I vs. CCC vs. type II EOC) were significant factors associated with PFS in the univariate and multivariate survival analyses. However, the histological subtypes were not significant factors related to OS in the multivariate survival analyses. CA-125 ≥ 200 units/ml, suboptimal surgery, FIGO stage II-IV, node metastasis, positive peritoneal cytology, and chemotherapy less than six cycles were found to be poor prognostic factors for PFS and OS. The coexistence with endometriosis was a significant factor associated with PFS but not a significant factor with OS.

Table 4. Univariate and multivariate survival analysis for progression-free survival.

Variables	n	Event (%)		Univariate analysis			Multivariate analysis		
				cHR	95% CI	p value	aHR	95% CI	p value
Histology									
Non-CCC type I EOC	69	16	(23.2)						
CCC	63	25	(39.7)	2.16	1.15-4.07	0.016	2.38	1.17-4.82	0.016
Type II EOC	81	48	(59.2)	3.91	2.20-6.93	< 0.001	2.20	1.14-4.24	0.019
Age									
< 60 yrs.	164	66	(40.2)						
> 60 yrs.	49	23	(46.9)	1.36	0.84-2.19	0.207			
Nulliparity									
No	131	65	(49.6)						
Yes	82	24	(29.3)	0.48	0.30-0.77	0.002	0.95	0.37-2.43	0.922
Menopausal status									
Premenopause	78	24	(30.8)						
Postmenopause	135	65	(48.1)	1.89	1.18-3.03	0.008	3.57	1.01-12.56	0.048
RMI									
< 200	33	11	(33.3)						
≥ 200	101	53	(52.5)	1.85	0.97-3.55	0.064	0.33	0.07-1.50	0.152
CA125									
< 200	49	13	(26.5)						
≥ 200	78	50	(64.1)	3.40	1.84-6.28	< 0.001	2.69	0.77-9.36	0.118
Optimal surgery									
No	49	36	(73.5)						
Yes	164	53	(32.3)	0.21	0.14-0.33	< 0.001	0.20	0.04-0.89	0.035
FIGO 2014 staging									
Stage I	120	28	(23.3)						
Stage II-IV	93	61	(65.6)	4.85	3.07-7.65	< 0.001	2.76	1.53-4.95	0.001
Associated endometriosis									
No	171	78	(45.6)						
Yes	40	9	(22.5)	0.42	0.21-0.84	0.014	1.08	0.32-3.57	0.895
Node metastasis									
Negative	152	51	(33.5)						
Positive	22	13	(59.1)	2.93	1.57-5.47	0.001	0.77	0.11-5.36	0.792
Peritoneal cytology									
Negative	95	32	(33.7)						
Positive	63	36	(57.1)	2.39	1.48-3.86	< 0.001	0.85	0.30-2.41	0.770
Chemotherapy cycles									
< 6 cycles	33	21	(63.6)						
≥ 6 cycles	152	65	(42.8)	0.47	0.29-0.78	0.003	0.32	0.81-1.28	0.109

cHR: crude hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, EOC: epithelial ovarian cancer, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: risk of malignancy index, FIGO: International Federation of Gynecology and Obstetrics

Table 5. Univariate and multivariate survival analysis for progression-free survival.

Variables	n	Event (%)		Univariate analysis			Multivariate analysis		
				cHR	95% CI	p value	aHR	95% CI	p value
Histology									
Non-CCC type I EOC	69	14	(20.3)						
CCC	63	17	(27.0)	1.69	0.83-3.43	0.150	1.81	0.88-3.69	0.105
Type II EOC	81	32	(39.5)	2.67	1.41-5.05	0.003	1.10	0.56-2.15	0.784
Age									
< 60 yrs.	164	46	(28.0)						
≥ 60 yrs.	49	17	(34.7)	1.49	0.85-2.61	0.161			
Nulliparity									
No	131	48	(36.6)						
Yes	82	51	(62.2)	0.46	0.25-0.83	0.010	0.44	0.13-1.49	0.190
Menopausal status									
Premenopause	78	18	(23.1)						
Postmenopause	135	45	(33.3)	1.65	0.95-2.85	0.074	5.79	1.09-30.73	0.039
RMI									
< 200	33	6	(18.2)						
≥ 200	101	38	(37.6)	2.35	0.99-5.58	0.052	0.10	0.01-1.06	0.056
CA125									
< 200	49	8	(16.3)						
≥ 200	78	37	(47.4)	3.62	1.68-7.81	0.001	7.94	0.92-68.09	0.059
Optimal surgery									
No	49	30	(61.2)						
Yes	164	33	(20.1)	0.20	0.12-0.34	< 0.001	0.47	0.26-0.85	0.012
FIGO 2014 staging									
Stage I	120	15	(12.5)						
Stage II-IV	93	48	(51.6)	6.14	3.41-11.04	< 0.001	4.67	2.28-9.57	<0.001
Associated endometriosis									
No	171	55	(32.2)						
Yes	40	6	(15.0)	0.43	0.19-1.00	0.051	3.43	0.66-17.54	0.140
Node metastasis									
Negative	152	32	(21.1)						
Positive	22	9	(40.9)	2.93	1.38-6.21	0.005	2.89	0.30-27.71	0.356
Peritoneal cytology									
Negative	95	17	(17.9)						
Positive	63	32	(50.8)	3.64	2.02-6.57	< 0.001	1.00	0.26-3.80	0.991
Chemotherapy cycles									
< 6 cycles	33	18	(54.5)						
≥ 6 cycles	152	43	(28.3)	0.37	0.21-0.34	< 0.001	0.15	0.29-0.86	0.033

cHR: crude hazard ratio; aHR: adjusted hazard ratio, CI: confidence interval, EOC: epithelial ovarian cancer, CCC: clear cell carcinoma, NCC: non-clear cell carcinoma, RMI: Risk of malignancy index, FIGO: International Federation of Gynecology and Obstetrics

Discussion

The incidence of CCC was 29.6% in the current study, which was consistent with previous data from Thai and Asian studies[12-15]. Several social and environmental factors may be the causes of higher incidences of CCC among Asians. Also, the increased amounts of endometriosis found in Asian women may have a role in elevating the incidence of CCC in Asia[16-18]. Previous reports have shown that CCC was the most common histologic subtype associated with endometriosis[19, 20] which goes in line with this study. Moreover, 74.6% of CCC presented with stage I that more common than NCC, which was also similar to the data from previous studies[6-9, 12-15].

In this study, CCC had a lower median value of serum CA-125 and RMI score than NCC. Currently, no clear benefit of such screening had been demonstrated in the high-risk group for ovarian cancer[21, 22]. CA-125 blood level elevated in approximately 80% of patients with FIGO stage II-IV but less than 50% with clinically detectable stage I disease[23-26].

Our study found that the PFS and OS in CCC and NCC groups were not significantly different. Many investigators have studied and compared the prognosis of patients with CCC to NCC, but conflicting results have been reported[7-9, 12, 13]. Several works of the literature showed the outcome of CCC being similar to other types of EOC. In contrast, others demonstrated a less successful outcome which a variety of factors could explain studied such as patients, chemotherapeutic regimens, and the proportion of suboptimal treatment[12, 13].

Nowadays, new insights into molecular genetics and histopathology can better understand ovarian carcinogenesis and its role in tumour classification[11]. Type I includes low-grade serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas, while type II comprises high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas. The type I tumours are generally low grade except for CCC, which is usually considered to be a high grade[24]. The grading was used to divide EOC into type I and II, which had clear evidence that influenced the prognosis[11, 27-29]. PFS and OS were significantly different from this study when OC was classified into 3 groups; NCC type I, type II EOC, and CCC. The NCC type I had the best survival outcomes, while type II EOC had the worst. Suppose the NCC group consists of a higher proportion of type II patients, especially the high-grade serous adenocarcinoma, which yields a poor prognosis. In that case, the result may produce better survival outcomes for CCC than NCC.

Similarly, if the NCC group has a higher proportion of type I patients, especially the low-grade serous adenocarcinoma and mucinous carcinoma, which provides a good prognosis, CCC's survival outcomes may be worse than NCC. The findings in this study confirmed this hypothesis that the PFS and OS of CCC and NCC were not statistically different when compared between CCC and NCC. However, if the CCC was separately classified as type I and type II EOC, the prognosis of CCC would change, which might signal physicians to allow more provision during ovarian cancer treatment.

The standard treatment of EOC involves aggressive debulking surgery followed by chemotherapy. Postoperative chemotherapy is indicated in all patients with EOC, except those with surgical pathologic stage I disease with low-risk characteristics[24]. Previously, adjuvant chemotherapy was offered to CCC patients in all stages[24]. In our study, all patients with CCC received adjuvant chemotherapy. Although the PFS of CCC stage I was better than type II EOC, the OS was not statistically different, which concurred with the current recommendation of the European Society for Medical Oncology-European Society of Gynaecological Oncology (ESMO-ESGO) consensus conference and Scottish Intercollegiate Guidelines Network (SIGN) suggesting that the benefit of adjuvant chemotherapy for patients with CCC stage I is uncertain and should be considered on an individual patient basis[30]. A large review of CCC demonstrated a poor outcome of advanced-stage CCC than serous epithelial ovarian cancer, which was also in agreement with the non-profit research organizations (NRG) oncology/ gynecologic oncology group, who reported decreased OS its inherent chemo-resistance of CCC[31].

Moreover, molecular genetics revealed that PIK3CA and AT-Rich Interaction Domain 1A (ARID1A) mutations were found in CCC while BRCA mutation and TP53 mutation were found in HGSC[11]. In our study, the 5-yr OS of CCC displayed a lower amount than in type II EOC. Every patient received paclitaxel and carboplatin chemotherapy for EOC. Therefore, the proper treatment of EOC should incorporate distinct molecular biology as a part of a therapeutic strategy in conjunction with standard chemotherapy to achieve the ultimate goal of therapy.

Advanced stage and suboptimal surgery have been extensively reported as poor prognostic factors[31-32]. In this study, suboptimal surgery, FIGO stage II-IV, node metastasis, positive peritoneal cytology, and received

chemotherapy less than six cycles were found to be poor prognostic factors for both PFS and OS. Therefore, the meticulous exploration of the pelvic and abdominal cavity for an optimal cytoreductive surgery at the first operation combined with proper adjuvant chemotherapy and continuing until six courses are the essential processes for staging and treatment[24].

Conclusion

In conclusion, the study showed that the prevalence of CCC was 29.65% of EOC patients, and the majority was found in the FIGO stage I. The PFS and OS were not statistically different between CCC and NCC. However, PFS and OS of NCC type I EOC was the best, while type II EOC was the worst outcomes when classified EOC into three groups: NCC type I, type II EOC, and CCC. Survival outcomes of CCC were located between NCC type I and type II EOC. This study emphasized the fact that the optimal surgery and complete course of platinum-based chemotherapy were the notable factors associated with better survival outcomes in patients with epithelial ovarian cancer.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Gestational Diabetes Mellitus in Pregnancy with Single Abnormal Value of 100-Gram Oral Glucose Tolerance Test at a Tertiary Hospital in Thailand

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ABSTRACT

Objectives: To determine the incidence of gestational diabetes mellitus (GDM) in pregnancy with a single abnormal value of the 100-gram oral glucose tolerance test (OGTT) after repeating for 1 month and to compare adverse pregnancy outcomes between pregnant women with a single abnormal value of the 100-gram OGTT and those with a normal 100-gram OGTT.

Materials and Methods: The retrospective cohort study was conducted from 1 August 2018 until 30 May 2021. Three hundred twenty-four pregnant women with a single abnormal value of 100-gram OGTT were recruited into a study group, while 365 pregnant women with normal 100-gram OGTT were recruited into a control group. In the study group, we repeated the second OGTT within one month to determine the incidence of GDM. Maternal and perinatal outcomes were then compared between the two groups.

Results: The incidences of GDMA2 and GDMA1 in pregnancy with a single abnormal test were 7.1% and 25%, respectively. Between the two groups, pregnancies in the study group were older (34.4 ± 7.3 vs. 29.3 ± 6.7, $p < 0.001$). Gestational hypertension (1 (0.3%) and 8 (2.5%), $p = 0.027$) and neonatal hypoglycemia (6 (1.6%) and 18 (5.6%), $p = 0.005$) were the adverse outcome that was higher in the study group with statistical differences.

Conclusion: Pregnant women with a single abnormal value of 100-gram OGTT developed a high incidence rate of GDM, gestational hypertension and neonatal hypoglycemia.

Keywords: 100-gram glucose tolerance test, gestational diabetes mellitus, incidence, one abnormal value, adverse pregnancy outcomes.

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ภาวะเบาหวานที่เกิดขึ้นขณะตั้งครรภ์ที่ตรวจพบค่าน้ำตาลผิดปกติหนึ่งค่าจากการตรวจความทนทานต่อน้ำตาล 100 กรัมที่โรงพยาบาลระดับตติย-ภูมิในประเทศไทย

พิมพ์ชนก พึ่งเสมา, สิริพร ไตรนาค

บทคัดย่อ

วัตถุประสงค์: *เพื่อหาอุบัติการณ์ของภาวะเบาหวานขณะตั้งครรภ์ที่ตรวจความทนทานต่อน้ำตาล 100 กรัม ที่พบค่าผิดปกติหนึ่งค่าหลังจากตรวจซ้ำภายในหนึ่งเดือน และผลการตั้งครรภ์ที่ไม่พึงประสงค์*

วัสดุและวิธีการ: *การศึกษาย้อนหลังตั้งแต่วันที่ 1 สิงหาคม 2561 ถึงเดือน 30 พฤษภาคม 2564 แบ่งหญิงตั้งครรภ์จำนวน 324 คนที่มีพบความผิดปกติจากการตรวจความทนทานต่อน้ำตาล 100 กรัม 1 ค่าเป็นกลุ่มศึกษา และหญิงตั้งครรภ์ 365 คนที่ผลการตรวจความทนทานต่อน้ำตาล 100 กรัมปกติเป็นกลุ่มควบคุม โดยหญิงตั้งครรภ์ในกลุ่มศึกษาจะได้รับการตรวจความทนทานต่อน้ำตาล 100 กรัมซ้ำภายในหนึ่งเดือนเพื่อหาอุบัติการณ์การเกิดภาวะเบาหวาน และเปรียบเทียบภาวะแทรกซ้อนของมารดาและทารกในหญิงตั้งครรภ์ทั้งสองกลุ่ม*

ผลการศึกษา: *อุบัติการณ์ของภาวะเบาหวานชนิด GDMA1 และ GDMA2 ในสตรีตั้งครรภ์ที่ตรวจความทนทานต่อน้ำตาล 100 กรัมและพบความผิดปกติหนึ่งค่าเท่ากับร้อยละ 25 และร้อยละ 7.1 ตามลำดับ กลุ่มศึกษามีอายุมากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (34.4 ± 7.3 vs. 29.3 ± 6.7, p < 0.001) ภาวะความดันโลหิตสูงที่ไม่พบโปรตีนในปัสสาวะ (1 (ร้อยละ 0.3) and 8 (ร้อยละ 2.5), p = 0.027) และภาวะน้ำตาลต่ำในเด็กแรกเกิด (6 (ร้อยละ 1.6) and 18 (ร้อยละ 5.6), p = 0.005) เป็นภาวะแทรกซ้อนที่พบในกลุ่มศึกษามากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ*

สรุป: *การตรวจความทนทานต่อน้ำตาล 100 กรัมขณะตั้งครรภ์ที่พบความผิดปกติหนึ่งค่า มีโอกาสเกิดเบาหวานขณะตั้งครรภ์และภาวะความดันโลหิตสูงที่ไม่พบโปรตีนในปัสสาวะ และการเกิดภาวะน้ำตาลต่ำในเลือดทารกแรกเกิดได้มากขึ้น*

คำสำคัญ: *การตรวจความทนทานต่อน้ำตาล 100 กรัม, ภาวะเบาหวานขณะตั้งครรภ์, อุบัติการณ์, ความผิดปกติหนึ่งค่า, ภาวะแทรกซ้อนของการตั้งครรภ์*

Introduction

Gestational diabetes mellitus (GDM) is a condition of carbohydrate intolerance that develops during pregnancy[1]. In Southeast Asian countries, including Thailand, the highest prevalence of GDM was reported with a median estimate of 29.2%[2]. GDM is associated with several negative maternal and neonatal complications, including hypertension, an increased rate of cesarean section, fetal macrosomia, neonatal hypoglycemia, and shoulder dystocia[3]. Furthermore, half of the women with GDM during pregnancy can develop type 2 diabetes mellitus 5-10 years post-delivery[2].

Diagnostic tests of GDM can be classified as one-step and two-step tests. It is recommended that all pregnant women should be tested for GDM (use patient clinical risk factors). If the 50-g glucose challenge test (GCT) is positive (≥ 140 mg/dL), a 100-g oral glucose tolerance test (OGTT) should be performed. The threshold values used for the OGTT based on the criteria of Carpenter and Coustan are: fasting ≥ 95 mg/dL, 1-hour ≥ 180 mg/dL, 2-hour ≥ 155 mg/dL and 3-hour ≥ 140 mg/dL. At least two abnormal values are required for diagnosis[1,3].

There is currently no consensus on whether pregnant women with a single abnormal value of 100-g OGTT should be retested or treated the same as pregnant women with a normal 100-g OGTT. As a result, the purpose of this study was to find the incidence of GDM and adverse outcomes in pregnant women with a single abnormal value of 100-g OGTT.

Materials and Methods

A retrospective cohort study was conducted at Chonburi Hospital after gaining approval from the institutional review boards. Laboratory records and medical databases from 1 August 2018 to 30 May 2021 were reviewed.

Singleton pregnancy with antenatal care clinic attendance and delivery at Chonburi Hospital, performance of a 50-g GCT at gestational age (GA) 24-28 weeks, pregnancy confirmation before 22 weeks, no underlying diseases, repeat the 100-g OGTT within 1 month, and Asian ancestry were the inclusion criteria. Exclusion criteria included a previous history of GDM during a previous pregnancy, a first degree relative with diabetes mellitus, BMI ≥ 30 kg/m^2, underlying disease with diabetes mellitus and lethal congenital abnormalities.

The data were analyzed using IBM SPSS Statistic 26.0. The sample size was calculated based on a similar study carried out by Kang et al (1997) at Seoul National University Bundang Hospital, which showed the incidence of GDM after repeat 100-g OGTT (28.5%) in pregnant women who were screened for GDM at 24-28 weeks[4]. The number of pregnant women with single abnormal value of 100-g OGTT should be at least 314 with alpha 0.05.

Following Chonburi hospital's clinical practice guideline, screening for GDM is based on risk screening. Pregnant women with severe obesity, a first-degree family history of diabetes mellitus, a prior history of GDM, impaired glucose metabolism, or glucosuria should be tested early at an antenatal visit and reevaluated at GA 24-28 weeks if GDM is diagnosed at first visit.

Pregnant women without risk factors were screened for GDM with 50-g GCT at GA 24-28 weeks based on the inclusion criteria. If the result was abnormal (140 mg/dL), it had to be tested again with a 100-g OGTT within one month. According to Carpenter and Coustan's criteria, the cut-off values for fasting, 1, 2, and 3-hour blood glucose were 95, 180, 155, and 140 mg/dL respectively.

After diagnosis with GDM, the patient was referred to a nutritionist to adjust her diet and calories, an ophthalmologist to rule out diabetic retinopathy, and an endocrine specialist. Pharmacological methods are recommended if diet modification cannot maintain the fasting plasma glucose levels < 95 mg/dL or 2-hour postprandial plasma glucose < 120 mg/dL.

All pregnancies with a single abnormal 100-g OGTT were assigned to a study group, whereas those with an abnormal 50-g GCT but a normal 100-g OGTT were assigned to a control group. To determine the incidence of GDM in a pregnancy with a single abnormal 100-g OGTT, the test must be repeated within one

month.

Pre-pregnancy body mass index (BMI), maternal age, history of previous cesarean section, and parity were all recorded as baseline characteristics. The primary outcome was the occurrence of GDM in pregnancy after a single abnormal 100-g OGTT that was repeated after one month. Secondary outcomes were maternal and neonatal outcomes. Maternal outcomes included GA at delivery, route of delivery (including cesarean section, spontaneous vertex delivery, vacuum extraction), postpartum hemorrhage, hypertensive disorder of pregnancy (including preeclampsia with a severe feature, gestational hypertension). Preeclampsia with severe features was diagnosed when blood pressure ≥ 160/110 mmHg with proteinuria (urine protein: creatinine ratio ≥ 0.3). Gestational hypertension was defined as blood pressure ≥ 140/90 mmHg without proteinuria[6]. Neonatal outcomes included birth weight, Apgar score at 1 minute, 5 minutes, 10 minutes, birth weight ≥ 4,000 grams, intrauterine growth restriction (IUGR) (birth weight less than 10th percentile for GA at birth), neonatal hypoglycemia, neonatal intensive care unit (NICU) admission, and sick newborn (SNB) admission.

Maternal and neonatal outcomes were compared between the two groups using independent t test and chi square test. A p value < 0.05 was considered statistically significant.

Results

During the study period, 365 pregnant women with one abnormal value of 100-g OGTT were assigned to the study group, while 324 pregnant women with normal 100-g OGTT values were assigned to the control group.

Incidences of GDMA1 and GDMA2 after repeat 100-g OGTT within 1 month were 81 (25%) and 23 (7.1%) respectively, and incidences of normal value and one abnormal value were 140 (43.2%) and 80 (24.7%), respectively.

The maternal demographic characteristics data are shown in Table 1. The mean maternal age of the study group was significantly older than the control group (34.4 ± 7.3 and 29.3 ± 6.7, p < 0.001). The study group also had a previous history of the cesarean section more than the control group with statistically significant (52 (16%) and 38 (10.4%), p = 0.028). Parity and pre-pregnancy BMI were not different.

Table 1. Maternal demographic characteristics.

Characteristics	Control group (n = 365)	Study group (n = 324)	p value
Maternal age (years) ± SD	29.3 ± 6.7	34.4 ± 7.3	< 0.001
Parity			0.031
0	133 (36.4%)	88 (27.2%)	
1	150 (41.1%)	157 (48.5%)	
≥ 2	82 (22.5%)	79 (24.4%)	
Pre-pregnant BMI (kg/m^2)			0.156
< 18.5	4 (1.1%)	5 (1.5%)	
18.5 - 24.9	142 (38.9%)	148 (45.7%)	
25 - 29.9	219 (60%)	171 (52.8%)	
mean ± SD	25.8 ± 3.1	25.2 ± 3.5	0.164
History of previous cesarian section	38 (10.4%)	52 (16%)	0.028

SD: standard deviation, BMI: body mass index

Maternal outcomes are shown in Table 2. The rate of developing gestational hypertension was significantly higher in study group (1 (0.3%) and 8 (2.5%), p = 0.011). Other maternal outcomes including route of delivery, postpartum hemorrhage and preeclampsia with severe feature were not statistically different.

Table 2. Maternal outcomes.

	Control (n = 365)	Study (n = 324)	p value
Route of delivery			0.145
- Cesarian section	108 (29.6%)	105 (32.4%)	
- Spontaneous vertex delivery	254 (69.6%)	211 (65.1%)	
- Vacuum extraction	3 (0.8%)	8 (2.5%)	
Postpartum hemorrhage	4 (1.1%)	3 (0.9%)	0.824
Preeclampsia with severe feature	2 (0.5%)	6 (1.9%)	0.111
Gestational hypertension	1 (0.3%)	8 (2.5%)	0.011

Neonatal outcomes are shown in Table 3. Infants of the study group had a significantly higher rate of hypoglycemia than those with control group (6 (1.6%) and 18 (5.6%), p = 0.005). The study group also had higher rate of birth weight ≥ 4,000 grams (6 (1.6%) and 12 (3.7%), p = 0.091) than study group but no statistical significance. The other neonatal outcomes: Apgar at 1 minute, 5 minutes, 10 minutes, SNB admission, NICU admission, IUGR, and ventilation support were similar in both groups but also not statistically significant, while there was a significant difference of GA at delivery.

Table 3. Neonatal outcomes.

	Control (n = 365)	Study (n = 324)	p value
GA at delivery (weeks)	38.5 ± 1.8	37.3 ± 6.1	0.001
Apgar at 1 min			0.654
> 7	359 (98.4%)	320 (98.8%)	
≤ 7	6 (1.6%)	4 (1.2%)	
Apgar at 5 min			0.288
> 7	365 (100%)	323 (99.7%)	
≤ 7	0 (0%)	1 (0.3%)	
Apgar at 10 min			0.288
> 7	365 (100%)	323 (99.7%)	
≤ 7	0 (0%)	1 (0.3%)	
birthweight	3,122.9 ± 493.3	3,190.0 ± 470.8	0.069
NICU admission	6 (1.6%)	5 (1.5%)	0.916
SNB admission	20 (5.5%)	14 (4.3%)	0.483
birthweight ≥ 4,000 grams	6 (1.6%)	12 (3.7%)	0.091
IUGR	2 (0.5%)	2 (0.6%)	0.905
ventilation support	8 (2.2%)	9 (2.8%)	0.621
hypoglycemia	6 (1.6%)	18 (5.6%)	0.005

GA: gestational age, NICU: neonatal intensive care unit, SNB: sick newborn, IUGR: intrauterine growth restriction.

Discussion

In most cases, the pathophysiology of GDM is similar to that of type 2 diabetes, which is also an inability to achieve an adequate insulin response due to a significant decrease in insulin sensitivity. Pregnant women with single abnormal 100-g OGTT may have

some degree of impair insulin sensitivity so they could develop GDM later.

Another reason why pregnant women with a single abnormal 100-g OGTT develop GDM, according to Ferrara et al, was that a diagnosis of GDM based on Carpenter and Coustan criteria resulted in a 50% increase in the prevalence of GDM[11].

Nowadays, the current guidelines for the diagnosis of GDM in pregnancy are mainly classified as universal screening and selective screening based on risk factors. Selective screening based on risk factors performs poorly as a screening tool, with up to one-sixth of women with GDM diabetes being missed[12]. This may affect the primary outcome of this study.

Francesco et al reported that hypertensive disorders (preeclampsia and pregnancy-induced hypertension) were more common in pregnancy with a single abnormal value of 100-g OGTT[10]. While this study found that gestational hypertension was significantly higher in the study group, preeclampsia with severe features did not differ statistically. It is possible that the previous study did not perform a subgroup analysis, which explains the discrepancy.

Prior studies have shown that adverse pregnancy outcomes with a single abnormal value of 100-g OGTT represented adverse neonatal outcomes; macrosomia had a higher rate in pregnancy with a single abnormal value of 100-g OGTT[7, 9-10] as well as a higher mean birth weight[7, 8]. The study group, on the other hand, had a higher birth weight of 4,000 grams, but the difference was not statistically significant.

There may be various reasons for the disparity in outcomes. First and foremost, this study was conducted in a moderate risk pregnancy group, and the study population was diverse. Second, because the sample size was calculated primarily for the primary outcomes (incidence of GDM in pregnancy with one abnormal value 100-g OGTT after repeat within 1 month), the sample size may be insufficient to represent the true adverse maternal and neonatal outcomes. Third, previous research has linked a single abnormal 100-g OGTT value to an increase in adverse neonatal outcomes, particularly macrosomia[7, 9-10]. Physicians have paid attention to and provided intensive counseling to this group, as they did to the GDM group. This emphasizes the importance of pregnant women getting adequate exercise and a diet plan in order to reduce the negative outcomes. Even though one-third of pregnant women with a single abnormal value of 100-g OGTT developed GDM, it seemed to have no clinical significance because the adverse outcomes of this group were not different from those with normal OGTT. Several biases may have affected the outcomes of this study.

The retrospective design study was the study's limitation. As a result of the previously hospital records' information, the data could be inaccurate and out of date. The strength of this study was the first interested in the incidence of GDM in the average-risk pregnancy group with one abnormal value after repeating within one month.

According to the result of this study, the incidences of GDMA1 and GDMA2 were 25% and 7.1% respectively. It showed a high incidence of GDM in pregnant women who had a single abnormal 100-g OGTT and then repeated it within one month. This could be used to develop clinical practice guidelines for the early detection of GDM in pregnancy at other hospitals. It may also reduce the adverse consequences of GDM.

This study suggested that pregnancy with a single abnormal 100-g OGTT value after repeating within one month tended to develop into GDM, particularly GDMA1, and increased the likelihood of pregnancy-induced hypertension, particularly gestational hypertension. As a result, obstetricians should be concerned about the planned diet program for this group and monitor their blood pressure during the antepartum and intrapartum periods.

Conclusion

Pregnant women with a single abnormal value of 100-gram OGTT developed a high incidence rate of GDM, gestational hypertension and neonatal hypoglycemia.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Lidocaine Prilocaine Cream versus Intracervical Injection for Pain Relief during Loop Electrosurgical Excision Procedure

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ABSTRACT

Objectives: To compare the effectiveness between lidocaine prilocaine cream versus intracervical injection for pain relief during loop electrosurgical excision procedure (LEEP).

Materials and Methods: Sixty women who underwent LEEP at Khon Kaen Hospital were enrolled in a single, blinded, non-inferiority randomized controlled trial. The participants were randomly allocated into two groups; group 1 received lidocaine prilocaine cream applied to the cervix (n = 30), and group 2 intracervical injection (n = 30) before performing LEEP. The pain score was measured at speculum placement, during anesthetization, during the procedure, immediately after, and 30 min after the procedure, using the 10-cm visual analogue scale (VAS). In addition, we recorded adverse events and additional analgesia.

Results: Baseline characteristics were similar between groups. The mean pain score during LEEP among groups was not significantly different between intracervical injections (control group) (5.53 ± 0.46, 95% confidence interval (CI) 4.60-6.47 vs. 4.59 ± 0.44, 95%CI 3.68-5.50, p = 0.145). The mean pain score during anesthetization with lidocaine prilocaine cream (intervention group) was significantly lower than with the intracervical injection (1.20 ± 0.29, 95%CI 0.60-1.80 vs. 3.62 ± 0.48, 95%CI 2.64-4.60, p < 0.001). No serious adverse events occurred.

Conclusion: Lidocaine prilocaine cream was not significantly different intracervical injection for pain relief during LEEP and provided better pain relief during anesthetization (than in the control group) without serious adverse events.

Keywords: loop electrosurgical excision procedure, LEEP, lidocaine prilocaine cream, intracervical injection, visual analog scale.

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ผลของการทาครีมยาชาเปรียบเทียบกับการฉีดยาที่ปากมดลูกเพื่อลดความเจ็บปวดในการตัดปากมดลูกด้วยห่วงไฟฟ้า

กชนิภา แพทยานันท์, ชินวัฒน์ ศรีนิล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลการลดความเจ็บปวดในผู้ป่วยที่เข้ารับการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า โดยการทาครีมยาชาเปรียบเทียบกับการฉีดยาชาที่ปากมดลูก*

วัสดุและวิธีการ: *สตรีที่เข้ารับการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าที่โรงพยาบาลขอนแก่น จำนวน 60 คน ถูกสุ่มแบ่งเป็นสองกลุ่ม คือ กลุ่มที่ 1 ได้รับการทาครีมยาชาที่ปากมดลูก และกลุ่มที่ 2 ได้รับการฉีดยาชาที่ปากมดลูกก่อนทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า สตรีทั้งสองกลุ่มได้รับการประเมินความเจ็บปวดขณะใช้เครื่องมือถ่างขยายช่องคลอด ขณะฉีดยาชาที่ปากมดลูกหรือทาครีมยาชาที่ปากมดลูก ระหว่างทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า หลังทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าเสร็จทันที และหลังทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าเสร็จนาน 30 นาที โดยใช้เครื่องมือวัดความเจ็บปวดประกอบด้วยเส้นตรงยาว 10 เซนติเมตร รวมถึงมีการประเมินภาวะแทรกซ้อนจากการใช้ยาและความต้องการยาแก้ปวดชนิดอื่นเพิ่มเติม*

ผลการศึกษา: *ข้อมูลลักษณะพื้นฐานทางประชากรศาสตร์ของทั้งสองกลุ่มไม่แตกต่างกัน คะแนนความเจ็บปวดระหว่างการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าในกลุ่มที่ทาครีมยาชาที่ปากมดลูก (กลุ่มทดลอง) ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติกับกลุ่มฉีดยาชาที่ปากมดลูก (กลุ่มควบคุม) (ค่าเฉลี่ยคะแนนความเจ็บปวด ± ส่วนเบี่ยงเบนมาตรฐานของกลุ่มทดลอง และกลุ่มควบคุมมีค่า 5.53 ± 0.46, 95%CI 4.60-6.47 เทียบกับ 4.59 ± 0.44, 95%CI 3.68-5.50, p = 0.145) แต่พบว่า คะแนนความเจ็บปวดระหว่างการให้ยาบรรเทาความเจ็บปวดก่อนทำหัตถการในกลุ่มที่ทาครีมยาชาที่ปากมดลูก (กลุ่มทดลอง) น้อยกว่ากลุ่มฉีดยาชาที่ปากมดลูก (กลุ่มควบคุม) (ค่าเฉลี่ยคะแนนความเจ็บปวด ± ส่วนเบี่ยงเบนมาตรฐานของกลุ่มทดลอง และกลุ่มควบคุมมี 1.20 ± 0.29, 95%CI 0.60-1.80 เทียบกับ 3.62 ± 0.48, 95%CI 2.64-4.60, p < 0.001) อย่างมีนัยสำคัญทางสถิติ และไม่พบภาวะแทรกซ้อนที่รุนแรงในทั้งสองกลุ่ม*

สรุป: *ประสิทธิภาพในการบรรเทาความเจ็บปวดระหว่างการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าในกลุ่มที่ทาครีมยาชาที่ปากมดลูกไม่แตกต่างจากกลุ่มควบคุม แต่การทาครีมยาชาที่ปากมดลูกสามารถลดความเจ็บปวดระหว่างให้ยาบรรเทาความเจ็บปวดก่อนทำหัตถการได้อย่างมีนัยสำคัญทางสถิติ และไม่พบภาวะแทรกซ้อนที่รุนแรงจากการใช้ยา*

Introduction

Since 1990, loop electrosurgical excision procedure (LEEP) has been used worldwide for the diagnosis and treatment of cervical intraepithelial neoplasia (CIN 2-3)[1-3]. The procedure is an invasive cervical procedure requiring effective pain control. Pain during LEEP is thought to result from heat generated during the excision. The generator combines high-frequency, low-voltage electric current that arcs between the loop (electrode) and the tissue it contacts. When current heats the cellular water content to boiling, cellular disruption and vaporization occurs, forming the plane of excision[4]. Several anesthetic techniques are used for pain relief during LEEP, including intracervical injection[5], topical anesthesia[6-7], and paracervical block (P.B.)[8]. Local anesthesia can be used to prevent pain; however, the standard of local anesthesia when performing LEEP remains unclear[4].

Lidocaine intracervical injection is routinely performed at Khon Kaen Hospital but it is invasive and causes bleeding that may interfere with colposcopic inspection. Lidocaine prilocaine cream is a new anesthetic agent widely used for local pain control for various procedures. Its advantages include non-invasive, easy-to-use, and less systemic absorption. It is also used for pain control in gynecologic procedures. The author was thus interested in conducting research comparing the effectiveness of pain control between the two anesthetic techniques.

The 5% Emla® cream comprises two local anesthetics - lidocaine 25 mg/g and prilocaine 25 mg/g. When 5% Emla® cream is applied onto a mucous membrane, absorption is rapid, so occlusive dressings are unnecessary. The onset of action is 5 min after application. The total maximum dosage is 20 g and the maximum recommended duration of exposure is 4 h. The percentage of absorption depend on skin surface blood flow[9,10]. One study reported that lidocaine prilocaine cream applied onto the uterine cervix before hysterosalpingogram (HSG) can relieve pain during the procedure. The cervical intervention was the most painful step during the procedure, and lidocaine prilocaine cream decreased the pain during this step[12]. It has also been used locally on the uterine cervix before laser ablation and hysteroscopy and was found to reduce pain[13,14].

The objective of the current study was to evaluate the efficacy of lidocaine prilocaine cream vs. intracervical injection for pain reduction during loop electrosurgical excision procedure (LEEP). The primary outcome was mean pain score during LEEP, and the secondary outcomes were (a) mean pain score (i) during speculum placement, (ii) during anesthetization, (iii) immediately after the procedure, (iv) 30 min after the procedure, (b) adverse events; and, (c) the need for additional analgesia.

Materials and Methods

The present study was a randomized, single-blinded, placebo-controlled trial. The Khon Kaen Hospital Institutional Review Board for Human Research reviewed and approved the study (KEF63018). All participants had the study explained to them and signed informed consent before enrolling.

We recruited 60 women 18 years or older who underwent LEEP at Khon Kaen Hospital between December 2020 and August 2021 after being diagnosed with cervical intraepithelial neoplasia. We excluded women with coagulopathy, neurological diseases with impaired sensation, cardiac arrhythmia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, lidocaine hypersensitivity, and those who were pregnant.

The participants were randomized into two groups using a computer-generated block of four: the study group - lidocaine prilocaine cream, and the control group - intracervical injection. The randomization list was kept in a sealed opaque envelope. Gynecologic oncologists performed LEEP.

The participants were first placed in a lithotomy position, and the operative area was cleaned and draped. Next, a sterile bivalve speculum was inserted into the vaginal canal to evaluate the uterine cervix. The operator determined the proper loop size to be used (1, 1.5, 2, 2.5, to 3 cm in diameter) based on the size, extent of the cervical lesion, and contour of the cervix under colposcopy. The study group received

5 g of 5% lidocaine prilocaine cream applied onto the cervix and external os using a cotton swab. The control group received 2% lidocaine with 1:100,000 epinephrine injected submucosally 1.8 ml (36 mg) at 3, 6, 9, and 12 o'clock of the ectocervix. After waiting for 5 min, LEEP was performed. The pain score was recorded using a 10-cm long, unmarked continuous horizontal line as a visual analog scale (VAS) for five different time points (speculum placement, during anesthetization, during excision, immediately after the procedure, and 30 min after the procedure). Patients were informed that the far-left point represented "no pain" and the far-right point represented "unbearable pain." They were then asked to mark the vertical line across the VAS five times to determine their pain levels. All participants could ask for additional analgesia when needed.

Vital signs and adverse events-i.e., lightheadedness, palpitation, numbness of lips, and tinnitus - were recorded by a nurse until 30 min after the procedure. Additional analgesia was also recorded. The primary outcome was the pain score during LEEP. The secondary outcomes were (a) the pain score (i) during speculum placement, (ii) during anesthesia, (iii) immediately after the procedure, (iii) 30 min after the procedure, (iv) 30 min after the procedure; (b) adverse effects; and, (c) the need for additional analgesia. In addition, baseline characteristics were recorded, including age, body mass index (BMI), parity, cervical cytology results, loop diameter, underlying disease, operative time, and pain score after applying the speculum.

The sample size was calculated based on data from the pilot study with 80% power at the 5% significance level with up to 10% dropout.

$Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.84$, 80% power

Pilot study: $\mu 1 = 5.38$, $\mu 2 = 6.29$

alpha = 0.05, beta = 0.2

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

The total sample size was thus 60 participants (30 in each group). Data were analyzed using STATA version 13. Continuous variables were analyzed using the student t-test and presented as means ± standard deviation (SD). Categorical variables were analyzed using the Chi-square or Fisher's exact test and presented as percentages. A p value < 0.05 was considered statistically significant.

Results

Sixty women were indicated as needing to undergo LEEP at Khon Kaen Hospital. All of the participants were recruited into the study and randomly allocated into two groups - the study group (lidocaine prilocaine cream) (n = 30) and the control group (intracervical injection) (n = 30). No dropouts occurred during the study, so the data from all 60 women were included and analyzed (Fig. 1).

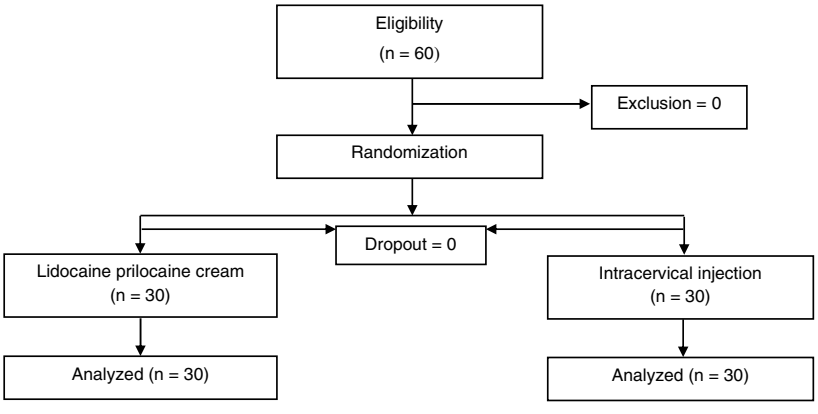

Fig. 1. Study flow diagram.

Both groups had similar demographics and characteristics, including age, BMI, menopausal status, parity, cervical cytology results, final histology, loop diameter, underlying diseases, operation time, and pain score after applying the speculum (Table 1).

Table 1. Demographics and characteristics of the cases.

	Lidocaine Prilocaine cream (n = 30)	Intracervical injection (n = 30)	p value
Age, y, Mean ± SD	38.87 ± 9.53	42.00 ± 10.71	0.236[c]
BMI, Mean ± SD, cm/m^2	23.22 ± 4.10	24.69 ± 3.66	0.149[c]
Menopausal status, n (%)			0.278[a]
Pre-menopause	27 (90.0)	24 (80.0)	
Menopause	3 (10.0)	6 (20.0)	
Parity, n (%)			0.739[a]
Nullipara	6 (20.0)	5 (16.7)	
Multipara	24 (80.0)	25 (83.3)	
Cervical cytology results			0.762[b]
ASC-H	3 (10.0)	6 (20.0)	
LSIL	7 (23.3)	4 (13.3)	
HSIL	17 (56.8)	15 (50.0)	
Cancer	1 (3.3)	1 (3.3)	
AIS	0 (0.0)	0 (0.0)	
AGC	1 (3.3)	2 (6.7)	
Other	1 (3.3)	2 (6.7)	
Final histology, n (%)			0.385[b]
CIN-1	2 (6.6)	3 (10.0)	
CIN-2	6 (20.0)	11 (36.7)	
CIN-3	17 (56.8)	12 (40.0)	
AGC	3 (10.0)	3 (10.0)	
AIS	0 (0.0)	0 (0.0)	
CIS	0 (0.0)	1 (3.3)	
Cancer	2 (6.6)	0 (0.0)	
Loop diameter, cm, Mean ± SD	1.70 ± 0.50	1.72 ± 0.43	0.891[c]
Underlying diseases, n (%)			
Hypertension	1 (3.33)	4 (13.3)	0.161[a]
Diabetes mellitus	1 (3.33)	3 (10.0)	0.301[a]
HIV	2 (6.6)	2 (6.6)	1.000[a]
Allergy	1 (3.3)	3 (10.0)	0.301[a]
Operative time, min, Mean ± SD	14.13 ± 1.63	10.50 ± 0.77	0.050[c]
Pain score after applied speculum Mean ± SD	1.64 ± 0.39	1.73 ± 0.40	0.877[c]

chi-square test[a], Fisher's Exact test[b], student t-test[c]

SD: Standard deviation, BMI: body mass index, ASC-H: atypical squamous cells cannot excluded HSIL, LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion, AIS: adenocarcinima in situ, AGC: atypical glandular cells, CIS: carcinoma in situ, CIN: cervical intraepithelial lesion, HIV: human immunodeficiency virus

The primary and secondary outcomes are presented in Table 2. The mean pain score was not significantly different between the study and control group during LEEP (5.53 ± 0.46, 95%CI 4.60 - 6.47 vs. 4.59 ± 0.44, 95%CI 3.68 - 5.50, p = 0.145); immediately after the procedure (1.45 ± 0.40, 95% CI 0.64 - 2.26 vs. 1.26 ± 0.31, 95%CI 0.62 - 1.90, p = 0.708); and 30 min after the procedure (2.13 ± 0.40, 95%CI 1.31 - 2.96 vs. 1.52 ± 0.36, 95%CI 0.79 - 2.25, p = 0.257).

Table 2. Primary and secondary outcomes.

VAS pain score	Lidocaine Prilocaine cream (n=30)	Intracervical injection (n=30)	Mean different	95% CI	p value
during anesthetization					< 0.001[c*]
mean ± SD	1.20 ± 0.29	3.62 ± 0.48	-2.41	-3.54 - 1.29	
(95% CI)	(0.60 - 1.80)	(2.64 - 4.60)			
During excision					0.145[c]
mean ± SD	5.53 ± 0.46	4.59 ± 0.44	0.94	-0.33 - 2.22	
(95% CI)	(4.60 - 6.47)	(3.68 - 5.50)			
Immediate after procedure					0.708[c]
mean ± SD	1.45 ± 0.40	1.26 ± 0.31	0.19	-0.82 - 1.20	
(95% CI)	(0.64 - 2.26)	(0.62 - 1.90)			
30 minutes after procedure					0.257[c]
mean ± SD	2.13 ± 0.40	1.52 ± 0.36	0.62	-0.46 - 1.70	
(95% CI)	(1.31 - 2.96)	(0.79 - 2.25)			
Cervical view					0.011[c*]
mean ± SD	98.00 ± 6.10	93.00 ± 8.37	5.00	1.22 - 8.78	
(95% CI)	(95.72 - 100.28)	(89.88 - 96.12)			

student T-test[c], significant p < 0.05*

VAS: visual analog scales, CI: confidence interval, SD: standard deviation

The mean pain score during anesthetization was significantly lower in the study group than in the control group (1.20 ± 0.29, 95%CI 0.60 - 1.80 vs. 3.62 ± 0.48, 95%CI 2.64 - 4.60, p < 0.001); and the cervical view was significantly better in the study group than in the control group (98.00 ± 6.10, 95%CI 95.72 - 100.28 vs. 93.00 ± 8.37, 95%CI 89.88 - 96.12, p = 0.011).

Only one woman in the study group experienced dizziness after applying the lidocaine prilocaine cream. One participant in the study group requested additional analgesia (Table 3).

Table 3. Adverse events and additional analgesia.

	Lidocaine Prilocaine cream (n=30)	Intracervical injection (n=30)	p value
Adverse events, n (%)			
Dizziness	1 (3.3)	0 (0.0)	0.500[b]
Additional analgesia, n (%)	1 (3.3)	0 (0.0)	0.500[b]
Bleeding, n (%)	2 (6.6)	0 (0.0)	0.246[b]

Fisher's Exact test[b]

Discussion

The mean pain score during LEEP in the lidocaine prilocaine cream group was not significantly different from that of the intracervical injection group (5.53± 0.46 vs. 4.59 ± 0.44). Adverse effects were not significantly different between the groups.

Although there has not been any study on the efficacy of lidocaine prilocaine cream for pain reduction during LEEP, previous studies on cervical and uterine interventions provided relevant comparisons. Liberty et al[10] reported on the effect of applying lidocaine prilocaine cream on the uterine cervix for pain relief after performing hysterosalpingography (HSG) in 84 women who underwent HSG as part of an infertility evaluation. Liberty et al[11] found that cervical instrumentation in the lidocaine prilocaine-treated patients was associated with significantly less pain than the placebo (3.3 ± 2.9 vs. 4.9 ± 2.7, p = 0.02).

Tavakolian et al[14] reported on the effect of lidocaine prilocaine cream on the uterine cervix to determine intrauterine device (IUD) insertion pain among 92 women who underwent IUD insertion. Tavakolian et al[14] found that lidocaine prilocaine cream significantly reduced pain during the use of a tenaculum compared with placebo (1.52 ± 1.85 vs. 4.30 ± 2.40, p < 0.001). In addition, the mean pain score during insertion of a hysterometer in the lidocaine prilocaine cream group was associated with significantly less pain than the placebo group (3.11 ± 2.53 vs. 5.20 ± 2.31, p < 0.001).

Williams et al[15] reported on the use of lidocaine-prilocaine cream for vulvar biopsy among 106 women undergoing vulvar biopsy. They found the cream significantly reduced pain before vulvar biopsy compared with a lidocaine injection (2 (0, 17) vs. 17 (5, 38), p = 0.02) with no significant difference pain at vulva biopsy (6 (1, 50) vs. 3 (0, 15), p = 0.47). Our study results thus agreed with these three previous studies[10, 14,15], indicating that lidocaine prilocaine cream reduced pain during LEEP.

Based on the current study, the difference in pain scores did not exceed the margin of clinical significance with less pain during anesthetization and significantly improved the cervical view. A better cervical view is key to the success of the procedure. Bleeding from intracervical injection might cause a poor cervical view and affect the adequacy of the procedure.

Besides the primary outcome, we found that the pain scores at speculum placement, immediately after LEEP, and 30 min after LEEP were not significantly different between groups. Lidocaine prilocaine cream produced the most prolonged duration of analgesia (about 45 min) and reduced pain scores (30 min after LEEP).

One of the participants in the lidocaine prilocaine cream group requested additional analgesia. There was no significant difference in adverse events between the two groups. Only one participant in the study experienced dizziness after the application of the lidocaine prilocaine cream. The symptom was mild and resolved within a few minutes without medical treatment. Zilbert[12] reviewed the effect of using lidocaine prilocaine cream for pain relief during minor gynecological procedures and found that it was well-tolerated and adverse reactions were generally mild, local, and transient.

Post-procedure bleeding was not significantly different between groups. However, two participants in the lidocaine prilocaine cream group noticed post-procedure bleeding. The mechanism of the post-procedure bleeding might be from the absence of any vasoconstriction effect of adrenaline.

The mean difference in operative time was 3.63 min, which was not significantly different between the lidocaine prilocaine cream and intracervical injection group (14.13 ± 1.63 and 10.50 ± 0.77, p = 0.05, respectively). This longer operative time might be due to the waiting time after lidocaine prilocaine cream application but not from any adverse event(s) after the intervention.

The study's strengths were that (a) it was randomized controlled trial, and (b) no patients dropped out. The limitations of the study were that (a) it was a single centre, blind intervention; and, (b) it lacked a cost-effectiveness analysis.

Conclusion

Compared with intracervical injection, lidocaine prilocaine cream (a) not significantly reduced pain during LEEP; (b) significantly reduced pain during anesthetization; and, (c) provided a better cervical view without any serious adverse event.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Pregnancy Outcomes in Term Pregnancy with Isolated Oligohydramnios

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ABSTRACT

Objectives: To compare birth asphyxia between term pregnant women with isolated oligohydramnios and normal amniotic fluid (AFI).

Materials and Methods: A retrospective cohort study was conducted in pregnant women who delivered in Charoenkrung Pracharak Hospital from January 1st, 2018, to December 31st, 2020. Obstetrics data and neonatal outcomes were noted among 756 women. Pregnancy outcomes in term pregnancy with isolated oligohydramnios of all 252 pregnant women (study group) were compared to those 504 pregnant women and low-risk pregnancy with normal amniotic fluid index (control group) in 1:2 ratio.

Results: The mean of gestational age of all participants was 38.63 ± 1.03 weeks. The mean AFI were 3.72 ± 1.21 cm and 10.73 ± 2.96 cm in the study and control groups, respectively. Isolated oligohydramnios (study group) was associated with a higher rate in nulliparous (46.4% vs 37.4%, p = 0.014) than in the control group. Moreover, pregnant women with isolated oligohydramnios had a significantly higher incidence of birth asphyxia (4% vs 1.4%, p = 0.024), neonatal intensive care unit admission (5.6% vs 0.4%, p < 0.001), and sick newborn admission (21% vs 13.1%, p = 0.005). There was a higher incidence of primary cesarean section in the study group when compared to the control group (30.6% vs 12.3%, p < 0.001). The justification of the higher rate of cesarean section in the study group was non-reassuring fetal heart rate status (14.7% vs 2.6%, p = 0.001) and failed medical induction (8% vs 1.2%, p = 0.001) when compared to the control group.

Conclusion: Isolated oligohydramnios in term pregnancy significantly increased the risk of birth asphyxia at 1 min and incidence of cesarean section.

Keywords: term pregnancy, isolated oligohydramnios, birth asphyxia, cesarean section.

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ผลลัพธ์การตั้งครรภ์ในสตรีตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำน้อยอย่างเดียว

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บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบภาวะการขาดออกซิเจนของทารกแรกเกิดระหว่างสตรีตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำน้อยอย่างเดียวและสตรีตั้งครรภ์ที่มีน้ำคร่ำปกติ*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลัง โดยศึกษาในสตรีที่คลอดบุตรที่โรงพยาบาลเจริญกรุงประชารักษ์ในช่วง 1 มกราคม พ.ศ.2561 - 31 ธันวาคม พ.ศ.2563 เป็นจำนวน 756 คน โดยเก็บข้อมูลการตั้งครรภ์ ข้อมูลการคลอด และข้อมูลทารกแรกคลอดของหญิงตั้งครรภ์นั้น และทำการคำนวณและเปรียบเทียบผลของทารกในหญิงตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำน้อยและหญิงตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำปกติ โดยแบ่งกลุ่มอัตราส่วน 1:2 การศึกษาในครั้งนี้จะศึกษาในหญิงตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำน้อยทั้งหมด 252 ราย และมีหญิงตั้งครรภ์ครบกำหนดที่มีภาวะน้ำคร่ำ 504 ราย*

ผลการศึกษา: *สตรีตั้งครรภ์ที่เข้าร่วมงานวิจัยมีอายุครรภ์เฉลี่ยเท่ากับ 38.63 ± 1.03 สัปดาห์ โดยในกลุ่มศึกษามีค่าเฉลี่ยดัชนีน้ำคร่ำ 3.72 ± 1.21 ซม. กลุ่มเปรียบเทียบมีค่าเฉลี่ยดัชนีน้ำคร่ำ 10.73 ± 2.96 ซม. การศึกษานี้พบว่าสตรีตั้งครรภ์แรกพบจำนวนสตรีตั้งครรภ์ที่มีภาวะน้ำคร่ำน้อย มากกว่าสตรีตั้งครรภ์ที่มีน้ำคร่ำปกติ (ร้อยละ 46.4 vs 37.4, p = 0.014) อย่างมีนัยสำคัญทางสถิติ จากการศึกษาผลลัพธ์ของการตั้งครรภ์พบว่า สตรีตั้งครรภ์ที่มีน้ำคร่ำน้อยพบ ภาวะขาดออกซิเจนของทารกแรกเกิด (ร้อยละ 4 vs 1.4, p = 0.024) การนอนหอผู้ป่วยทารกวิกฤต (ร้อยละ 5.6 vs 0.4, p < 0.001) การนอนหออภิบาลทารกป่วย (ร้อยละ 21 vs 13.1, p = 0.005) อัตราการผ่าตัดคลอดครั้งแรก (ร้อยละ 30.6 vs 12.3, p < 0.001) และสาเหตุการผ่าตัดเนื่องจากอัตราการเต้นของหัวใจทารกในครรภ์ผิดปกติ (ร้อยละ 14.7 vs 2.6, p = 0.001) และการชักนำให้เกิดการเจ็บครรภ์ด้วยยาล้มเหลว (ร้อยละ 8 vs 1.2, p = 0.001) มากกว่าสตรีที่ที่มน้ำคร่ำปกติอย่างมีนัยสำคัญทางสถิติ*

สรุป: *มารดาที่ตั้งครรภ์ครบกำหนดที่มีน้ำคร่ำน้อยเปรียบเทียบกับมารดาที่ตั้งครรภ์ครบกำหนดที่มีน้ำคร่ำปกติ มีอัตราการเกิดภาวะขาดออกซิเจนในทารกแรกคลอดที่ 1 นาทีหลังคลอด และเพิ่มอัตราการผ่าตัดคลอดอย่างมีนัยสำคัญทางสถิติ*

คำสำคัญ: *การตั้งครรภ์ครบกำหนด, ภาวะน้ำคร่ำน้อย, ภาวะขาดออกซิเจนทารกแรกคลอด, การผ่าตัดคลอด*

Introduction

Amniotic fluid[1] is important in pregnancy for maintaining balanced fluid, electrolyte and body temperature of the fetus. To help the development of muscle, bone, lungs and avoid compression to the fetus in utero, amniotic fluid is produced about 12 days after fertilization from maternal blood flow through the placenta. Then after 8-11 weeks, the fetus begins to produce urine, which becomes a component of amniotic fluid. Fetal urine is the main component of amniotic fluid after 18 weeks of gestation. If the fetus has a urinary tract disorder such as a congenital kidney, this will reduce the amount of amniotic fluid[2]. Usually, amniotic fluid volume increases gradually to the maximum during 36 weeks of gestation, after that, the amniotic fluid volume decreases after 40 weeks of gestation[3]. Ultrasonography is high-efficacy method to measure the amniotic fluid index (AFI)[4]. When the AFI is < 5 cm or the deep vertical pocket (DVP) is < 2 cm, it is defined as oligohydramnios. When the AFI is > 25 cm or DVP is > 8 cm, it is defined as polyhydramnios[5].

Isolated oligohydramnios (IO)[6] is oligohydramnios without congenital anomaly, fetal growth restriction (FGR)[7], intraamniotic infection and maternal complications [such as pregnancy induce-hypertension (PIH), preeclampsia, diabetes mellitus, abruptio placenta, chronic kidney disease, systemic lupus erythematosus (SLE), and antiphospholipid syndrome (APS)]. These conditions decrease blood supply to multiple organs and kidneys; therefore, the fetus produces less urine and resulting in oligohydramnios. The maternal complications which associated with abnormal blood vessel formation may reduce blood flow and oxygen between the placenta and fetus and result in oligohydramnios. Thus, the isolated oligohydramnios is not directly related to maternal and fetal complication as already mentioned.

Oligohydramnios is a common pregnancy complication, and the incidence is approximately 0.5 - 5% of all pregnancies[8]. The degree of oligohydramnios is proportional to the severity of placental hypoperfusion from the reducing maternal blood flow to the placenta, affect fetal growth restriction. Furthermore, oligohydramnios in the third trimester causes the condition of non-reassuring fetal status from external fetal monitoring due to umbilical cord compression, meconium aspiration syndrome, asphyxia[9], high incidence of Neonatal intensive care unit (NICU) admission[10] and fetal death[11]. Early detection of oligohydramnios can reduce the risk of fetal death or neonatal death[12, 13].

The prevalence of neonatal death is approximately 15-30%[14], and birth asphyxia is the main cause[15]. The prevalence of oligohydramnios which is the main cause of birth asphyxia is 11.5%[16]. From the previous study, isolated oligohydramnios is associated with a higher rate of cesarean section, birth asphyxia[17], and NICU admission. However, from the other studies[18], there was no significant difference in the incidence of birth asphyxia and cesarean section in the pregnant women with isolated oligohydramnios when compared to the normal pregnant women.

The incidence of birth asphyxia in Charoenkrung Pracharak hospital is approximately 5-10%. Consequently, we want to study whether isolated oligohydramnios can potentially impact adverse pregnancy outcomes or not. Therefore, the objectives of this study were to determine the pregnancy outcomes, such as rate of birth asphyxia and cesarean section between pregnant women with isolated oligohydramnios and pregnant women with normal amniotic fluid.

Materials and Methods

We performed a retrospective cohort study after the ethical committee approved the research proposal of the Medical Service Department, Bangkok Metropolitan Administration. The data of pregnant women who delivered in Charoenkrung Pracharak Hospital from January 1st, 2018 to December 31st, 2020 were reviewed from medical

chart records and electronic databases.

In that period, we collected the data from term singleton pregnant women who had the evidence of ultrasonographic assessment of AFI and delivered in Chareonkrung Pracharak Hospital. The study group included the pregnant women who had isolated oligohydramnios from the ultrasonographic report (AFI < 5 cm.). The control group consisted of low-risk term pregnancies with a normal amount of amniotic fluid (AFI 5-25 cm), delivered on the same day as the study case. The exclusion criteria included: (1) premature rupture of membranes, (2) multifetal pregnancy, (3) death fetus in utero/still birth, (4) pregnancy with major fetal malformation, (5) pregnant women with obstetrics complications such as hypertensive disorders, diabetes, an autoimmune disease, (6) fetal growth restriction (defined as a sonographic estimated fetal weight below the 10th percentile according to gestation), (7) polyhydramnios (AFI > 25 cm), and (8) incomplete medical record.

All pregnant women in the study and control groups had sonographic documentation of AFI level 1 week before the delivery and completed all medical records. Data were obtained from the admission chart record. The following demographic and obstetrical variables were recorded: maternal age, gravidity, parity, the number of antenatal care (ANC), prior cesarean deliveries, gestational age at delivery, the interpretation of intrapartum external fetal monitoring in the form of reassuring or non-reassuring fetal heart rate status (normal fetal heart rate 120-160 beats/min), and route of delivery. The following neonatal outcomes were collected: Apgar scores at 1 and 5 min (Apgar score at 1 min less or equal to 7 according to World Health Organization (WHO)[19] and Apgar score at 5 min less than 7 according to American College of Obstetricians and Gynecologists (ACOG)[17], birth weight, perinatal morbidity, and perinatal mortality.

From the previous study by Asnafi[21], the sample size was calculated by the incidence of birth asphyxia in pregnant women with oligohydramnios (5.7%) and pregnant women with normal AFI (1.7%). This study used the ratio of 1:2 for the study group and the control group in the same period, 252 pregnant women from term pregnancy with isolated oligohydramnios group and 504 pregnant women from term pregnancies with normal AFI were required. Data were analyzed by parametric and nonparametric statistics using SPSS version 26 (IBM Corp., Armonk, NY). Descriptive statistics, including means, standard deviations, percentages and numbers, appropriately described various characteristics, as appropriate. Various characteristics were compared between the groups using the chi-squared test, or the Mann-Whitney U test, as appropriate. Results were considered statistically significant if $p < 0.05$.

Results

From January 1st, 2018, to December 31st, 2020, there were 9,818 pregnant women delivered at Charoenkrung Pracharak Hospital. Of these, 756 pregnant women were enrolled. We collected 252 pregnant women with isolated oligohydramnios (study group) and 504 pregnant women with a normal amount of amniotic fluid (control group).

Table 1 provides the maternal demographic data. This study showed the mean gestational age of all participants was 38.63 ± 1.03 weeks. The mean AFI values were 3.72 ± 1.21 cm and 10.73 ± 2.96 cm in the study and control groups, respectively. The mean pre-pregnancy body mass index (BMI) in the study group was higher than the control group (26.18 ± 6 vs 21.37 ± 3.63, $p < 0.001$). Isolated oligohydramnios (study group) had a higher number of nulliparous (46.4% vs 37.4%, $p = 0.014$) than the control group. There was no significant difference in the mean gestational age of pregnant women between groups.

The obstetric outcomes are shown in Table 2. The pregnant women with isolated oligohydramnios had significantly higher incidence of primary cesarean section (30.6% vs 12.3%, $p < 0.001$), repeated cesarean section (25% vs 16.7%,

p < 0.001), primary cesarean section due to non-reassuring fetal heart rate status (14.7 % vs 2.6%, p = 0.001) and failed medical induction (8% vs 1.2%, p = 0.001) when compared to the control group. But the control group had a higher incidence of the cesarean section from cephalopelvic disproportion (CPD) (7.9 % vs 8.5%, p < 0.001) than study group. However, there was no significant difference in postpartum hemorrhage between both groups.

Table 1. Maternal demographic characteristics.

Characteristics	Oligohydramnios (n = 252)	Normal (n = 504)	p value
Age (year)	28.63 ± 6.46	27.47 ± 6.08	0.015
Gestational age (weeks)	38.54 ± 1.14	38.67 ± 0.97	0.120
Amniotic fluid index(cm)	3.72 ± 1.21	10.73 ± 2.96	< 0.001
Pre-pregnancy BMI (kg/m^2)	26.18 ± 6	21.37 ± 3.63	< 0.001
Parity			0.014
Nulliparous	117 (46.4%)	187 (37.1%)	
Multiparous	135 (53.6%)	317 (62.9%)	

Data are presented as mean ± standard deviation or n (%). BMI: body mass index

Table 2. Obstetric outcomes between pregnant women with isolated oligohydramnios and pregnant women with normal amniotic fluid.

	Oligohydramnios (n = 252)	Normal AFI (n = 504)	p value
Route of delivery			< 0.001
Vaginal delivery	112 (44.4)	358 (71)	
Primary Cesarean section	77 (30.6)	62 (12.3)	
Repeat Cesarean section	63 (25.0)	84 (16.7)	
Primary cesarean section from			0.001
CPD	20 (7.9)	43 (8.5)	
Fetal heart rate non-reassuring	37 (14.7)	13 (2.6)	
Failed medical induction	20 (8)	6 (1.2)	
Presentation			0.624
Vertex	239 (94.8)	482 (95.6)	
Breech	13 (5.2)	22 (4.4)	
Postpartum hemorrhage	14 (5.6)	50 (9.9)	0.052

Data are presented as n (%). AFI: amniotic fluid index, CPD: cephalopelvic disproportion

Table 3 shows the neonatal outcomes between groups. The mean birth weights were 2,975.39 ± 397.61 grams and 3,139.30 ± 366.51 grams in the study and control groups, respectively. The incidence of birth asphyxia at 1 min in the study group was significantly higher when compared to the control group (4% vs 1.4%, p = 0.024). Moreover, this study displayed a significantly higher incidence of NICU admission (5.6% vs 0.4%, p < 0.001) and sick newborn admission (21% vs 13.1%, p = 0.005) in the study

group compared to the control group. However, the incidence of asphyxia at 5 min, and meconium-stained amniotic fluid were not significantly difference between both groups.

Table 3. Neonatal outcomes between pregnant women with isolated oligohydramnios and pregnant women with normal amniotic fluid.

	oligohydramnios (n = 252)	Normal AFI (n = 504)	p value
Birth weight (grams)	2,975.39 ± 397.61	3,139.30 ± 366.51	< 0.001
Gender			0.719
Male	127 (50.4)	261 (51.8)	
Female	125 (49.6)	243 (48.2)	
Apgar 1 min (birth asphyxia)			
≤ 7	10 (4)	7 (1.4)	0.024
Apgar 5 min (birth asphyxia)			
< 7	1 (0.4)	1 (0.2)	1.000
Meconium stained			0.044
Mild	19 (7.5)	59 (11.7)	
Moderate	6 (2.4)	4 (0.8)	
Thick	1 (0.4)	0	
NICU admission	14 (5.6)	2 (0.4)	< 0.001
Sick newborn admission	53 (21)	66 (13.1)	0.005

Data are presented as mean ± standard deviation or n (%)
AFI: amniotic fluid index, NICU: Neonatal intensive care unit

Discussion

This study showed a significantly higher incidence of birth asphyxia at 1 min after delivery in pregnant women with isolated oligohydramnios than pregnant women with normal amount of amniotic fluid. This was consistent with the previous study by Asnafi[20] which showed a higher rate of birth asphyxia outcome due to oligohydramnios. Oligohydramnios affected fetus via pressure on the umbilical cord, resulting in fetal hypoxia and probably delivery of a neonate with birth asphyxia. Birth asphyxia was diagnosed on Apgar score at 1 min ≤ 7. The Apgar score at 1 min may represent intrapartum condition, and the 5-min Apgar score may represent the management of neonatal resuscitation. In this study, there was no significant difference of birth asphyxia at 5 min after delivery due to early activated management of neonatal resuscitate team then decreased rate of birth asphyxia at 5 min after delivery. However, AFI can be indicated for fetal well-being in pregnancy to detect fetuses at risk of adverse outcomes. This study showed a significantly high incidence of NICU admission and sick newborn ward admission. The high incidence of NICU and sick newborn ward admission were due to oligohydramnios which resulted in newborn with birth asphyxia and higher rates of intrapartum complication from non-reassuring fetal heart rate status then close monitoring in NICU and sick newborn ward was observed. In contrast, the previous studies by Ashwal[21] and Patel et al[11] showed no significant difference in both groups in the incidence of birth asphyxia and NICU admission, which discussed in this topic that isolated oligohydramnios in term pregnancy might be physiologically decreased in amniotic fluid volume from advanced gestation similar to in a normal pregnancy.

This study showed a significantly higher

incidence of cesarean section in pregnant women with oligohydramnios which was consistent with the study by Nankali[22]. The rate of primary cesarean section due to non-reassuring fetal heart rate status is significantly increased in pregnant women with isolated oligohydramnios because this condition causes umbilical cord compression that results in abnormal intrapartum fetal heart rate monitoring. The high incidence of primary cesarean section due to failed medical induction in this study was because we induced labor due to oligohydramnios status at $36^{0/7}$ - $37^{6/7}$ weeks of gestation[23] when the cervix was unfavorable for delivery. In contrast, the previous studies[24] reported no significant difference in the incidence of cesarean section in pregnant women with isolated oligohydramnios and normal amniotic fluid.

In this study, we found that isolated oligohydramnios in term pregnancy more common in the overweight group of pregnant women, however there was no scientific data to explain this association. In contrast, study by Blitz25 found no association between increased BMI and oligohydramnios.

A limitation of this study was that it was a retrospective, single center study. Strength of our study was that a few studies in Thailand have investigated pregnancy outcomes of isolated oligohydramnios in term pregnancy. This knowledge can be applied to provide close monitoring in antepartum and intrapartum pregnant women who have isolated oligohydramnios.

Conclusion

Isolated oligohydramnios in term pregnancy significantly increased the risk of birth asphyxia at 1 min and incidence of cesarean section.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Prevalence and Associated Factors of Anemia in Different Periods of Pregnancy

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ABSTRACT

Objectives: This study aimed to study the prevalence of anemia in the different period of pregnancy and also indicated precipitating factors that caused failure of anemia prophylaxis in antenatal care.

Materials and Methods: This was a longitudinal prospective study enrolled total 130 pregnant women who visit antenatal care (ANC) clinic from November 2020 to August 2021. A questionnaire was completed during the third trimester and complete blood count was evaluated at each period of pregnancy: in first ANC, during third trimester and intrapartum period. All data were analyzed by SPSS software (version 22.0).

Results: The prevalence of anemia in first ANC, third trimester and intra-partum was 6.92%, 24.62%, and 4.76% respectively. Poor compliance of iron supplementation and clinical morning sickness were associated with anemia in the third trimester of pregnancy.

Conclusion: Anemia in pregnancy remains an urgent public health problem in Thailand. Strict compliance with iron supplementation is vital for preventing anemia in pregnancy.

Keywords: anemia, pregnancy, iron supplementation, morning sickness, compliance, education.

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ความชุกและปัจจัยที่เกี่ยวข้อง ของภาวะโลหิตจางในแต่ละช่วงเวลาของการตั้งครรภ์

สุภเวช เลิศประสบสุข, บุษบา วิริยะสิริเวช

บทคัดย่อ

วัตถุประสงค์: *ภาวะโลหิตจางขณะตั้งครรภ์เป็นปัญหาทางด้านสาธารณสุขที่พบบ่อยในประเทศไทย วัตถุประสงค์ของงานวิจัยชิ้นนี้ คือ เพื่อศึกษาความชุกของภาวะโลหิตจางในระยะต่างๆ ของการตั้งครรภ์ และหาปัจจัยที่ทำให้การป้องกันภาวะโลหิตจางระหว่างการฝากครรภ์ล้มเหลว*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนา (แบบไปข้างหน้า) โดยผู้เข้าร่วมการวิจัยคือ สตรีตั้งครรภ์จำนวน 130 คน ที่มาฝากครรภ์ที่คลินิกฝากครรภ์ ของโรงพยาบาลวชิรพยาบาล ตั้งแต่ เดือนพฤศจิกายน พ.ศ.2563 ถึง เดือนสิงหาคม พ.ศ.2564 ผู้เข้าร่วมการวิจัยแต่ละคนจะต้องตอบแบบสอบถามในช่วงไตรมาสที่สามของการตั้งครรภ์ และได้รับการตรวจเลือด CBC (complete blood count) ตั้งแต่การฝากครรภ์ครั้งแรก, ระหว่างไตรมาสที่สามของการตั้งครรภ์ และระหว่างช่วงการคลอดตามลำดับ*

ผลการศึกษา: *ความชุกของภาวะโลหิตจางในช่วงการฝากครรภ์ครั้งแรก, ช่วงไตรมาสที่สามของการตั้งครรภ์ และช่วงระหว่างการคลอดที่ห้องคลอด คือ ร้อยละ 6.92, 24.62 และ 4.76 ตามลำดับ โดยที่ปัจจัยที่เกี่ยวข้องกับภาวะโลหิตจางในไตรมาสที่สามของการตั้งครรภ์อย่างมีนัยสำคัญคือ มีภาวะแพ้ท้องในช่วงไตรมาสแรกของการตั้งครรภ์ และไม่มีความสม่ำเสมอในการรับประทานธาตุเหล็กเสริมระหว่างตั้งครรภ์*

สรุป: *แม้ว่าความชุกของภาวะโลหิตจางในหญิงตั้งครรภ์ในกรุงเทพมหานครมีแนวโน้มลดลง แต่ก็ยังคงเป็นปัญหาทางสาธารณสุขที่สำคัญของประเทศไทย การรับประทานธาตุเหล็กเสริมตามที่แพทย์สั่งอย่างเคร่งครัด ช่วยลดโอกาสการเกิดภาวะโลหิตจางลงได้*

คำสำคัญ: *ภาวะโลหิตจาง, หญิงตั้งครรภ์, ธาตุเหล็กเสริม, ภาวะแพ้ท้อง, ความสม่ำเสมอในการรับประทานธาตุเหล็กเสริมระหว่างตั้งครรภ์*

Introduction

According to World Health Organization (WHO) criteria[1], anemia in pregnancy is defined as a blood hemoglobin level of below 11.0, 10.5, and 11.0 g/dL in the first, second, and third trimester, respectively. There are many causes of anemia. The first one is dilutional anemia, which occurs when the increase of blood plasma volume is greater than hemoglobin, causing hemoglobin level to decrease proportionally compared with non-pregnant women[2]. The second one is iron deficiency anemia. The prevalence of iron deficiency increases during pregnancy as women need a higher amount of iron after mid pregnancy. In addition, the patient may have an underlying condition that causes anemia, such as chronic renal disease and thalassemia. Anemia can affect both pregnant women and infants[3]. Hemoglobin transports oxygen throughout the body, as well as to the placenta. WHO reports that anemia increases maternal mortality rate, maternal sepsis, cesarean section rate, and blood transfusion rate. There is also an elevated risk of low birth weight and preterm birth in the fetus affected[4].

Nowadays, anemia in pregnancy is a global health problem, especially in developing countries. The WHO estimates that 40% of pregnant women are anemic. The prevalence of anemia in some areas of Thailand is estimated at 50% despite the efforts by health care workers to provide iron and folic acid supplements among pregnant women. With exception of iron deficiency, hemoglobinopathy, dilutional anemia, and other chronic diseases, anemia can also caused by other precipitating factors such as lifestyle, education, income per month, and duration of and compliance with iron supplement intake during pregnancy. Failure of anemia prophylaxis arises from these factors.

Cuneyt et al[5] reported that the prevalence of anemia in term pregnant women in Turkey was 41.6%, with the associated factors being parity, literacy, income per month, duration of iron supplement intake, and history of preeclampsia. In India, Suryanarayana et al[6] reported that the prevalence was 62.3%. Literacy was also an important factor. These reports demonstrated that anemia could cause fetal low birth weight, preterm birth and pregnancy induced hypertension significantly. Although there are several studies in Thailand which report the prevalence of anemia in pregnancy, the data on factors associated with anemia is still limited. These studies focus on the overall data of anemic pregnant women which do not exclude the data on those with thalassemia and anemia due to chronic disease. Siriwong et al[7] reported that the prevalence of anemia in pregnant women who visited the antenatal clinic in Mae-sot hospital was 49%. In 2003, Chotnopparatpattara et al[8] reported that the prevalence of anemia in pregnant women who visited the antenatal clinic in Chulalongkorn hospital was 14.8%, 20.5%, and 38.6% in the first, second and third trimester, respectively. In 2016, The Ministry of Public Health launched Thailand's antenatal care guidelines for health care workers[9] that provided a standard dose of iron supplements. Pregnant women thoroughly received iron supplementation to prevent anemia, but we have never reevaluated the prevalence of anemia again.

This research aimed to study the prevalence of anemia in the different periods of healthy pregnant women who received standard iron supplement program and indicated precipitating factors that cause the failure of anemia prophylaxis in the third trimester because the highest prevalence of anemia was found in the third trimester of pregnancy, the period of which we had sufficient time to correct an anemia before labor.

Materials and Methods

A longitudinal prospective study was carried out at the antenatal clinic, the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, a tertiary-care university hospital. The study was conducted in accordance with the ethical principles of the declaration of Helsinki, and the study protocol was approved by the Vajira Institutional Review Board. Informed consents were obtained from all subjects.

Study design and participants

This study recruited healthy singleton pregnant women in the third trimester of pregnancy who attended services at the antenatal clinic of Vajira Hospital, Bangkok, Thailand. In order to exclude any factors interfering with anemia results, the pregnant women enrolled in this study had to have a normal thalassemia screening result without any chronic disease.

The inclusion criteria were as follows: age over 18 years old, singleton pregnancy, gestational age more than 28 weeks, attending the antenatal clinic at Vajira Hospital, having evaluated with complete blood count before gestational age (GA) 20 weeks, having attended for the first antenatal care before GA 20 weeks, and having negative deichorophenol precipitation test (DCIP) result with an mean corpuscular volume (MCV) of more than 80 fl. The exclusion criteria were those with a chronic disease that can cause anemia, such as chronic kidney disease, autoimmune disease, HIV infection, etc.

All participants were provided with information explaining the objectives of the study before signing consent forms at the antenatal clinic. Then, the participants completed the questionnaire forms given to them. The questionnaire collected participants' information from the first trimester to the third trimester. Health care workers were ready to answer the participants any questions related to the questionnaire while the questionnaire was being completed. The complete blood count of each participant in the third trimester was collected at this visit and was collected again before labor. The complete blood count in the first ANC and related information were collected by the E-phis system of Vajira Hospital.

Outcome measures

Blood samples were collected from all pregnant women on the first day that they attended the ANC, during the third trimester, and during the intrapartum period, respectively. Gestational age was estimated using the date of last menstruation and the ultrasound scan measurements. The medical and obstetrical history (gravid, underlying disease, history of anemia, history of blood transfusion, and iron supplement), socioeconomic data, and demographic data were collected from the participants' information forms. Each participant's weight and height were measured in kilograms and centimeters, respectively. Then, each participant completed a self-questionnaire which consisted of questions related to the information nationality, history of morning sickness, compliance to iron supplementation, income per month, educational level, and their antenatal clinic appointment attendance.

Statistical analysis

The sample size was calculated using the formula for descriptive study. When the prevalence of anemia in the third trimester was 38.6%, and the level of significance (α) = 0.05 and d = 0.09, one hundred and twenty participants were required.

All data were analyzed by SPSS software (version 22.0). The data were presented as mean ± standard deviation (SD), number (%), or percentage (95% confidence interval (CI)) as appropriate. The quantitative measures are presented by mean and SD and qualitative variables by proportions. A comparison of the risk factors between anemic and non-anemic groups of pregnant women in the third trimester was performed using Chi-square statistics, with a p value less than 0.05 being considered statistically significant. The odds ratio (OR) with 95%CI was used to measure the strength of association between anemia and exposure variables.

The categorization of variables was as follow: (1) a pregnant woman was considered anemic if the hemoglobin level was < 11 g/dl, (2) the monthly income is categorized into 2 groups: < 10,000 bath and > 10,000 bath, (3) the maternal age was categorized into 2 groups: < 35 years old and ≥ 35 years old (based on the age of elderly primigravida mother)[10], (4) BMI (body mass index) was categorized into 4 groups: underweight, normal,

overweight, and obese, (5) the interpregnancy interval was categorized into 2 groups: < 5 years and ≥ 5 years (according to the report of a WHO technical consultation on birth spacing)[11], (6) the gestational age at the first antenatal care visit was categorized into 2 groups: ≤ 12 weeks and > 12 weeks (entering ANC after 12 weeks of gestation was considered late)[12, 13], (7) the gestational age at the initial stage of iron supplementation was categorized into 2 groups: ≤ 12 weeks and > 12 weeks (based on the recommendation by the Centers for Disease Control and Prevention (CDC) that iron supplementation should be initiated at the first antenatal visit)[14], (8) the weight gain in third trimester was categorized into 3 groups: <10 kg, 10-15 kg, and >15 kg (based on the recommendation for total and rate of weight gain during pregnancy)[10]. The compliance of iron supplementation was categorized in 2 groups: good compliance (> 80%) and poor compliance (< 80%).

Results

The demographic data of the participants were as follows. The participant's age (the total number of participants is 130) ranges from 18 to 42 years, with a mean age of 28.59 (SD 6.21) years. The majority of the participants (114 participants) were Thai (87.6%), 81 were multigravida (62%), 69 had normal weight (53%), 70 were secondary school graduated (53%), and 68 had a monthly income of 10,000 - 20,000 bath (52.3%). Fifty-two percent of multigravida reported an interpregnancy interval of more than 5 years. 85.4% of participants reported that they had received iron supplements at GA between 12-20 weeks, 63% reported that they had their first visit at the antenatal care clinic at GA before 12 weeks, and 84% had good compliance with iron supplements.

The prevalence of anemia in the first ANC, the third trimester, and the intrapartum period was 6.92%, 24.62% and 4.76%, respectively, as demonstrated in Table 1.

Table 1. Prevalence of anemia by period of pregnancy.

Period of pregnancy	n (%)	Hb mean ± SD (range)	Hct mean ± SD (range)
First ANC (n = 130)	9/130 (6.9%)	10.24 ± 0.33 (9.7 - 10.7)	31.74 ± 1.50 (28.5 - 33.1)
Third trimester (n = 130)	32/130 (24.6%)	10.58 ± 0.36 (9.5 - 10.9)	32.23 ± 1.21 (29.0 - 34.0)
Intrapartum (n = 94)	4/94 (4.3%)	10.35 ± 0.33 (10.1 - 10.8)	31.07 ± 0.93 (29.8 - 31.9)

ANC: antenatal care, Hb: hemoglobin, Hct: hematocrit, SD: standard deviation

Regarding the factors associated with anemia in Pregnancy, Table 2 demonstrates the associations between anemia in the third trimester and several predictor variables. Pregnant women who had poor compliance for iron supplements had six times higher odds of being anemic (OR 6.75, 95%CI 2.44-18.67) compared to pregnant women who had good compliance. Pregnant women who used to have morning sickness in the first trimester had 2.5 times higher odd of being anemic (OR 2.59, 95%CI 1.11-6.04) compared to pregnant women who never had morning sickness. Other factors including race, income per month, education, age, gravida, body mass index (BMI), inter-pregnancy interval, and GA at the first ANC were assessed, but they were not associated with anemia during the third pregnancy.

Table 2. Univariable analysis for factors associated with anemia in the third trimester of pregnancy.

Factors	Anemia Hb < 11 g/dL (n = 32)		No anemia Hb > 11 g/dL (n = 98)		OR	95%CI	p value
	n	(%)	n	(%)			
Race							
Thai	30	(93.8)	84	(85.7)	2.50	(0.54 - 11.65)	0.243
Other	2	(6.3)	14	(14.3)	1.00	Reference	
income							
< 10000 bath	11	(34.4)	43	(43.9)	1.00	Reference	
> 10000 bath	21	(65.6)	55	(56.1)	1.49	(0.65 - 3.43)	0.345
Education							
Secondary school or below	24	(75.0)	66	(67.3)	1.46	(0.59 - 3.59)	0.417
College school	8	(25.0)	32	(32.7)	1.00	Reference	
Age							
< 35 years old	25	(78.1)	81	(82.7)	1.00	Reference	
≥ 35 years old	7	(21.9)	17	(17.3)	1.33	(0.50 - 3.58)	0.567
Gravida							
Primigravidarum	13	(40.6)	36	(36.7)	1.18	(0.52 - 2.67)	0.694
Multigravida	19	(59.4)	62	(63.3)	1.00	Reference	
BMI							
Under weight	4	(12.5)	15	(15.3)	0.67	(0.19 - 2.36)	0.530
Normal range	14	(43.8)	35	(35.7)	1.00	Reference	
Overweight	6	(18.8)	14	(14.3)	1.07	(0.34 - 3.35)	0.906
Obese	8	(25.0)	34	(34.7)	0.59	(0.22 - 1.58)	0.293
Pregnancy interval							
< 5 years	9	(28.1)	25	(25.5)	1.35	(0.45 - 4.02)	0.590
> 5 years	8	(25.0)	30	(30.6)	1.00	Reference	
Unknown	15	(46.9)	43	(43.9)	1.31	(0.49 - 3.47)	0.590
GA at the first ANC							
< 12 weeks	19	(59.4)	64	(65.3)	1.00	Reference	
> 12 weeks	13	(40.6)	34	(34.7)	1.29	(0.57 - 2.92)	0.545
GA when first received iron supplements							
< 12 weeks	1	(3.1)	12	(12.2)	1.00	Reference	
> 12 weeks	31	(96.9)	86	(87.8)	4.33	(0.54 - 34.66)	0.168
Missing an appointment							
Never	29	(90.6)	90	(91.8)	1.00	Reference	
1 time	3	(9.4)	8	(8.2)	1.16	(0.29 - 4.68)	0.831
Morning sickness							
No	10	(31.3)	53	(54.1)	1.00	Reference	
Yes	22	(68.8)	45	(45.9)	2.59	(1.11 - 6.04)	0.027
Compliance with iron supplementation							
> 80%	20	(62.5)	90	(91.8)	1.00	Reference	
< 80%	12	(37.5)	8	(8.2)	6.75	(2.44 - 18.67)	< 0.001

Hb: hemoglobin, OR: odds ratio, CI: confidence interval, BMI: body mass index, GA: gestational age.

Discussion

The prevalence of anemia in third trimester pregnant women in this study was 24.6%. Other studies[7, 8, 15-17] reported that the prevalence of anemia in the third trimester of pregnancy was between 38.6% - 50%. Concerning the period of pregnancy, according to this study, the highest prevalence of anemia was among pregnant women in the third trimester and other studies[8, 15-17] also reported similar findings. However, in this study, the prevalence of anemia during the intrapartum period was much lower compared to that of the third trimester period. We suggested further study to explain the improvement of anemic status during the intrapartum period.

Pregnant women tended to be anemic more than non-pregnant women due to physiological change (dilutional effect) and increased iron consumption. Sukrat et al[17] demonstrated that the main causes of anemia during pregnancy were thalassemia carriers/ disease (54.9%) and iron deficiency (43.1%). Over the past year, the government has reinforced ANC service, leading to pregnant women thoroughly receiving iron supplementation to prevent anemia. However, the prevalence of anemia in Thailand is still high, which means that there are precipitating factors that have caused the failure of anemia prophylaxis in antenatal care. Several studies[5, 6, 18] reported that education and literacy were associated with anemia. Patients with higher education had less tendency to develop anemia than those without one. Taner et al[5] reported that the associated factors with anemia were parity, income per month, duration of iron supplementation, and the number of times visiting ANC. Siriwong et al[7] reported that nationality was associated with anemia. The prevalence of anemia in Burmese pregnant women was higher than in Thai pregnant women.

In this study, we found that compliance with iron supplementation and morning sickness were associated with anemia. Pregnant women who had good compliance with iron supplementation and didn't have clinical morning sickness were less likely to be anemic compared to their counterparts. Compliance with iron supplementation and morning sickness were closely relevant. Pregnant women who had nausea and vomiting also encountered poor drug compliance. Nasir et al[19] reported that forgetfulness and fear of side effects were the commonest reasons for poor adherence to IFAS (iron and folic acid supplementation) in Ethiopia. Fouelifack et al[20] reported that the reasons for non-adherence were side effects, forgetfulness, and inaccessibility of iron supplements in Cameroon. Kiwanuka et al[21] reported that inadequate drug supplies and fear of side effects were the main reasons why participants had not taken iron supplements in Uganda. As mentioned previously, poor compliance with iron supplementation arises not only because of patient behavior, but also from factors out of the patient's control. In Thailand, there was insufficient data exploring the causes of poor drug compliance.

Strict compliance with iron supplementation is believed to be vital for preventing anemia in pregnancy. Maternal misunderstanding about the iron supplement program should be corrected. Pregnant women should have awareness about anemia in pregnancy and the benefits of iron supplements. Sirisopa et al[22] reported that the pharmaceutical care program for pregnant women with iron deficiency anemia can play a role in the improvement of the iron deficiency status of Thai pregnant women. Health care providers must renew their commitment to iron therapy by monitoring and improving compliance.

Regarding the strength and weakness of this study, pregnant women who were enrolled in this study had a normal thalassemia screening result and didn't have any chronic disease that interfered with the anemic result. However, the sample size was too small to effectively analyze associated factors with anemia.

Conclusion

Anemia in pregnancy was a public health problem in Thailand. Prevalence of anemia in the third trimester of pregnancy was 24.6%. Poor compliance of iron supplementation and clinical morning sickness were associated with anemia in the third trimester of pregnancy. We suggested further study to explore the causes of poor compliance with iron supplementation

in Thailand.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

Prevalence of Abnormal Glucose Metabolism in Thai Women with Polycystic Ovary Syndrome

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ABSTRACT

Objectives: To assess the prevalence and associated factors of abnormal glucose metabolism (AGM) including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) in Thai women with polycystic ovary syndrome (PCOS).

Materials and Methods: A retrospective study was conducted in PCOS women who came to the Srinagarind Hospital, Khon Kaen University during 2014 - 2020. Glucose metabolism was determined by a 75-g oral glucose tolerance test. IFG, IGT, and DM were defined according to the American Diabetes Association 2021 criteria. Logistic regression analysis was applied to assess factors associated with AGM. The 95% confidence interval (CI) was calculated to determine the precision of results.

Results: Of 188 patients, AGM was noted in 65 PCOS women, accounting for the prevalence of 34.6 % (95%CI 28.1 - 41.7). Among those with AGM, 10.1%, 23.9%, and 4.8% were diagnosed with IFG, IGT and DM, respectively. Compared to those without AGM, PCOS women with AGM trended to have higher body mass index, waist circumference, waist to hip ratio, blood pressure, and triglyceride level. These clinical parameters and anthropometric measures however were not independently associated with AGM by mean of multiple logistic regression analysis.

Conclusion: Abnormal glucose metabolism was prevalent among PCOS women residing in the Northeast Thailand. Approximately 5% of PCOS women in this study were diagnosed with type 2 DM. Anthropometric measures were not independently associated with AGM.

Keywords: abnormal glucose metabolism, impaired fasting glucose, impaired glucose tolerance, diabetes mellitus, PCOS.

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ความชุกของภาวะการเผาผลาญน้ำตาลผิดปกติในสตรีไทยที่ได้รับการวินิจฉัยกลุ่มอาการถุงน้ำในรังไข่หลายใบ

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยที่เกี่ยวข้องของภาวะการเผาผลาญน้ำตาลผิดปกติ (abnormal glucose metabolism; AGM) ซึ่งประกอบด้วย ระดับน้ำตาลหลังงดน้ำและอาหารที่ผิดปกติ (impaired fasting glucose; IFG), ระดับน้ำตาลหลังกินน้ำตาล 2 ชั่วโมง ผิดปกติ (impaired glucose tolerance; IGT) และภาวะเบาหวาน (diabetes mellitus; DM) ในสตรีที่ได้รับการวินิจฉัยกลุ่มอาการถุงน้ำในรังไข่หลายใบ (Polycystic Ovary Syndrome; PCOS)*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลัง (Retrospective study) โดยเก็บรวบรวมข้อมูลในสตรีที่ได้รับการวินิจฉัย PCOS ซึ่งมารับบริการที่โรงพยาบาลศรีนครินทร์ในช่วง พ.ศ. 2557-2563 การเผาผลาญน้ำตาลกลูโคส (glucose metabolism) ประเมินโดนการตรวจ 75-g Oral Glucose Tolerance Test (OGTT) เมื่อมารักษาครั้งแรก ภาวะการเผาผลาญน้ำตาลผิดปกติวินิจฉัยโดยใช้เกณฑ์ของ the American Diabetes Association (ADA) 2021 ปัจจัยที่เกี่ยวข้องของภาวะดังกล่าววิเคราะห์โดยวิธี logistic regression*

ผลการศึกษา: *ในสตรีที่ได้รับการวินิจฉัย PCOS จำนวน 188 ราย พบความชุกของภาวะการเผาผลาญน้ำตาลผิดปกติใน 65 ราย คิดเป็นร้อยละ 34.6 (95%CI, 28.1-41.7) โดย ในสตรีร้อยละ 10.1, ร้อยละ 23.9 และร้อยละ 4.8 ตรวจพบภาวะ IFG, IGT และ DM ตามลำดับ สตรีที่มีภาวะการเผาผลาญน้ำตาลผิดปกติ มีระดับดัชนีมวลกาย, เส้นรอบเอว, เส้นรอบเอวต่อสะโพก, ความดันเลือด และไตรกลีเซอไรด์ สูงกว่าสตรีที่มีค่าน้ำตาลปกติ อย่างไรก็ดี ไม่พบความสำคัญทางสถิติ ของปัจจัยดังกล่าวต่อการเผาผลาญน้ำตาลผิดปกติ เมื่อวิเคราะห์ด้วยวิธี logistic regression*

สรุป: *ความชุกของภาวะการเผาผลาญน้ำตาลผิดปกติพบได้สูงในสตรีที่ได้รับการวินิจฉัย PCOS ในภาคตะวันออกเฉียงเหนือของไทย โดยพบสตรีที่มีภาวะเบาหวาน 5%*

คำสำคัญ: *ภาวะการเผาผลาญน้ำตาลผิดปกติ, ระดับน้ำตาลสูงในเลือด, ภาวะการทนต่อน้ำตาลบกพร่อง, โรคเบาหวาน, กลุ่มอาการถุงน้ำในรังไข่หลายใบ*

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in reproductive-aged women[1]. It is a complex disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology[2]. Apart from reproductive disturbance, women with PCOS carry higher risks of various metabolic disturbances, including diabetes mellitus, dyslipidemia, and cardiovascular disease[3,4].

Several hypotheses have been proposed to be the pathogenesis of PCOS, however the definite one has not been established. The pathophysiology of PCOS is complex and multifactorial involving endocrine, metabolic, genetic, epigenetic, and environmental factors[5]. Although insulin resistance is not a diagnostic criterion of PCOS, it may be central to the etiology of the syndrome[6]. Insulin resistance and compensatory hyperinsulinemia brings PCOS women to an increased risk of abnormal glucose metabolism (AGM). AGM consists of an impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM). The American Diabetic Association (ADA) recommends using a 75-g oral glucose tolerance test (OGTT) for investigating AGM[7]. Due to the fact that women with PCOS carry a higher risk of developing AGM, OGTT should be investigated for assessing glycemic status in all women with PCOS[3,8].

The prevalence of AGM among PCOS women varies according to the ethnicity of population assessed[9-13]. Asian, American, and European PCOS women carry 5, 4, and 3-fold increased risks of developing AGM[9,12,13]. To date, existing evidence regarding the prevalence of AGM among Thai women with PCOS are limited[14-17]. The prevalence of AGM among Thai women with PCOS varies widely across the regions, ranging from 20.0% to 45.9%[14-17]. T2DM, the most severe form of AGM, was noted in 5.6%-11.4% of Thai women with PCOS[14-17].

Since the cultural and food consumption behavior differ across the regions in Thailand which may have had a contributing effect on the glycemic status. The present study was accordingly undertaken with the aim to assess the prevalence and associated factors of AGM among PCOS women attending the gynecological endocrinology clinic at Srinagarind Hospital which is a tertiary hospital in Northeastern region of Thailand.

Materials and Methods

Study setting and participants

This study was a retrospective study conducted at the gynecological endocrinology clinic, Srinagarind Hospital, Khon Kaen University, Thailand. The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (HE631201). The data from reproductive-aged PCOS patients visiting the clinic between 2014-2020 were reviewed. A diagnosis of PCOS was based on the revised Rotterdam 2003 criteria[18]. Women who had been previously diagnosed with diabetes mellitus, dyslipidemia, or other endocrinologic abnormalities or had history of steroid or other hormonal usage or had incomplete medical records were excluded. The objectives of the present study were to investigate the prevalence and associated factors of AGM in PCOS women.

Data collection and variables of interest

The demographic and laboratory data from the computer-based medical records system were extracted and collected to add to the data collection form that one of the authors made, then transferred to Microsoft Excel program and double checked by another author for correctness before analysis. The variables of interest included age, body weight, height, body mass index (BMI), waist circumference, waist-to-hip ratio (WHR) and blood pressure. The results of plasma glucose level and lipid profiles that were obtained from initial visit of each woman were collected.

Glucose metabolism was determined by a 75-g OGTT. Abnormal plasma OGTT was classified according to the ADA 2021 criteria[7]. IFG was defined as fasting plasma glucose (FPG) levels from 100 to 125 mg/dl. IGT was defined as a 2-hour plasma glucose (2-h PG) levels from 140 to 199 mg/dl. T2DM was defined as FPG ≥ 126 mg/dl or 2-h PG ≥ 200 mg/dl. Prediabetes state is the term used for individuals who have IFG or IGT which glucose levels are higher than

normal but not meet the diagnostic criteria for T2DM. Prediabetes is a serious health condition as the majority of individuals with prediabetes will eventually develop diabetes.

Statistical analysis

Statistical analysis was performed using Stata program version 10. Descriptive statistics including mean (standard deviation), median (interquartile range), and number (percentage) were used to report the characteristics of the patients. Comparisons between the groups were performed using the student's t-test, Mann-Whitney U test, Chi-squared test, or Fisher's exact test when appropriate. The independent risk factors associated with AGM were assessed using multiple logistic regression analysis. The 95% confidence interval (CI) was calculated to determine the precision of results. $P<0.05$ was considered statistically significant.

Results

During the study period, a total of 188 PCOS women attending the gynecological endocrinology clinic, Srinagarind Hospital were reviewed. The results of OGTT are demonstrated in Table 1. AGM was detected in 65 women, accounting for the prevalence of 34.6% (95%CI 28.1% to 41.7%). Of these, 10.1% had IFG (95%CI 6.5% to 15.4%), 23.9% had IGT (95%CI 18.3% to 30.6%) and 4.8% had T2DM (95%CI 2.5% to 9.0%). Pre-diabetes state was found in 30.9% of women (95%CI 24.6% to 37.9%)

Table 1. Prevalence of abnormal glucose metabolism in 188 Thai women with polycystic ovary syndrome.

Abnormal glucose metabolism[1]	Prevalence	
	n	% (95% confidence interval)
Overall	65	34.6 (28.1 - 41.7)
Pre-diabetes state[2]	58	30.9 (24.6 - 37.9)
- Impaired fasting glucose (IFG)	19	10.1 (6.5 - 15.4)
- Impaired glucose tolerance (IGT)	45	23.9 (18.3 - 30.6)
Diabetes mellitus (DM)[3]	9	4.8 (2.5 - 9.0)
- Fasting plasma glucose ≥ 126 mg/dl	6	3.2 (1.4 - 7.0)
- 2-hour glucose ≥ 200 mg/dl[4]	9	4.8 (2.5 - 9.0)

[1] Abnormal glucose metabolism: impaired fasting glucose (fasting plasma glucose = 100-125 mg/dl), impaired glucose tolerance (2-hour glucose = 140-199 mg/dl), or diabetes mellitus (DM)

[2] Pre-diabetes state: impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (13 women had IFG, 39 women had IGT, and 6 women had combined IFG plus IGT)

[3] Diabetes mellitus: fasting plasma glucose ≥ 126 mg/dl or 2-hour glucose ≥ 200 mg/dl (3 women had 2-hour glucose ≥ 200 mg/dl and 6 women had combined fasting plasma glucose ≥ 126 mg/dl plus 2-hour glucose ≥ 200 mg/dl)

[4] 6 women had combined fasting plasma glucose ≥ 126 mg/dl plus 2-hour glucose ≥ 200 mg/dl, 2 women had IFG plus 2-hour glucose ≥ 200 mg/dl, and 1 woman had 2-hour glucose ≥ 200 mg/dl alone

Table 2 demonstrates the clinical and laboratory characteristics of 188 women with PCOS. In comparison to those without AGM, women with AGM had significantly higher body weight, BMI, waist circumference, WHR, blood pressure, and triglyceride (TG) level. High density lipoprotein (HDL) level was lower among women with AGM when compared to those without AGM.

The significant factors associated with increased risk of AGM among PCOS women were age ≥ 30 years, BMI ≥ 25 kg/m^2 and waist circumference ≥ 80 cm with odds ratio of 2.35 (95%CI 1.18 to 4.68), 2.26 (95%CI 1.21 to 4.22) and 2.06 (95%CI 1.10 to 3.87), respectively (Table 3). After adjusted factors with multiple logistic regression analysis, these associations however were not statistically significant.

Table 2. Characteristics of 188 Thai women with polycystic ovary syndrome with abnormal glucose metabolism and those with normal glucose metabolism.

Characteristics	All PCOS women (n = 188)	Abnormal glucose metabolism[1] (n = 65)	Normal glucose metabolism (n =123)	p value
Age (years)	24 (21-29)	25 (21-30)	24 (21-29)	0.343
Body weight (kilograms)	66 (53-81)	71 (58-87)	61 (51-79)	0.018
Height (centimeters)	159.9 ± 6.1	158 (156-166)	160 (156-163)	0.638
Body mass index (kg/m^2)	25 (21-31)	27 (23-31)	24 (20-30)	0.011
Waist circumference (centimeters)	80 (70-92)	85 (76-92)	80 (68-90)	0.013
Waist to hip ratio	82.9 ± 6.6	84.9 ± 6.0	81.7 ± 6.7	0.002
Systolic blood pressure	120.5 (110.5-133)	130 (115-137)	119 (108-130)	0.003
Diastolic blood pressure	73.8 ± 12.0	76.4±12.9	72.4±11.3	0.030
Hypertension[2]	10 (5.3%)	6 (9.2%)	4 (3.3%)	0.097
Family history of DM	51 (27.1)	21 (32.3%)	30 (24.4%)	0.246
Glucose metabolism				
Fasting plasma glucose (mg/dl)	88 (83-94.5)	97 (88-104)	86 (80-90)	< 0.001
2-Hour glucose (mg/dl)	116 (95-146.5)	158 (145-179)	102 (91-119)	< 0.001
Lipid profiles				
Total cholesterol	191.5 (172- 215.5)	188 (171-206)	196 (172-218)	0.184
HDL	56 (46-69.5)	50 (42-59)	60 (50-72)	0.001
LDL	129 (110.5-152)	126 (114-148)	134 (109-156)	0.676
Triglyceride	114 (81.5- 154)	125 (88-161)	111 (79-141)	0.030

Data are presented as mean ± standard deviation, median (interquartile range) and number (%)

PCOS: polycystic ovary syndrome, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low density lipoprotein

[1] Abnormal glucose metabolism: impaired fasting glucose (fasting plasma glucose = 100-125 mg/dl), impaired glucose tolerance (2-hour glucose = 140-199 mg/dl), or diabetes mellitus (DM)

[2] Hypertension: systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

Table 3. Risk factors for abnormal glucose metabolism (AGM) in 188 PCOS women.

Factors	OR (95% CI)[1]	Adjusted OR (95% CI)[2]
Age ≥ 30 years	2.35 (1.18 - 4.68) *	1.86 (0.89 - 3.88)
BMI ≥ 25 kg/m^2	2.26 (1.21 - 4.22) *	1.51 (0.53 - 4.26)
Waist circumference ≥ 80 cm	2.06 (1.10 - 3.87) *	1.27 (0.46 - 3.53)
Hypertension	3.03 (0.82 - 11.14)	-
Dyslipidemia	1.59 (0.77 - 3.28)	-

Data were analyzed using logistic regression analysis.

[1] simple logistic regression analysis

[2] multiple logistic regression analysis adjusted with all factors in this table

* p-value < 0.05

PCOS: polycystic ovary syndrome, OR: odds ratio, CI: confidence interval, BMI: body mass index

Discussion

Our study revealed that the prevalence of AGM in PCOS women residing in Northeastern region of Thailand was 34.6% (95%CI 28.1% to 41.7%). Among women who had AGM, 30.9% had pre-diabetes state which include IFG and IGT. T2DM was noted in 4.8% (95%CI 2.5% to 9.0%) of patients. Patients' age and anthropometric measures however were not independently associated with the risk of AGM.

The prevalence of pre-diabetes state and T2DM noted in our study appeared to be higher than that in general Thai female population. In a study of Aekplakorn et al[19], which was undertaken among Thai population aged ≥ 20 years during 2004-2014, the prevalence of IFG and T2DM in female aged 20 - 29-year-old were 8.9% and 2.9%, respectively. Findings of our study thus reaffirmed that PCOS women is a subset of women with an increased risk of developing glucose abnormality. Determining glycemic status, therefore, is an essential assessment for PCOS women[20]. Interestingly, our result showed that 67.2% of women with pre-diabetes state and 11.1% of those with T2DM did not have IFG. Determining fasting plasma glucose alone, therefore, is insufficient to diagnose AGM in all PCOS women. These findings supported the use of a 75-g OGTT as a screening tool for AGM among PCOS women.

To our knowledge, there were only four studies assessing the prevalence of AGM in Thai PCOS women[14-17]. Three studies were conducted in Bangkok and the remaining one in Chiang Mai. All the prior studies recruited reproductive-aged PCOS women according to the revised Rotterdam diagnostic criteria[18]. Albeit of the same ethnicity and PCOS phenotype, the prevalence of AGM reported in these studies varies widely. Our study revealed lower AGM prevalence than that reported by Charnvises et al[16] and Weerakiet et al[15], which were undertaken among PCOS women residing in Bangkok. These two previous studies found prevalence of AGM among PCOS women to be 42.9% and 45.9%, respectively. In comparison to the previous study conducted in Chiang Mai by Pantasri et al[17], the prevalence in our study was also lower. Pantasri et al reported that approximately 43% of PCOS women residing in Chiang Mai were noted to have AGM. The difference of AGM prevalence among Thai PCOS women noted in our study compared to previously reported findings may be due to the fact that the PCOS women in our study appeared to be younger and had lower BMI than that in previous reports, thus, carrying a lower risk of AGM.

Another one study was undertaken in Bangkok by Wongwananuruk et al[14]. Although comparable in age of study samples, the prevalence of AGM in our study was higher than that in Wongwananuruk et al (34.6% versus 20%, respectively). The higher prevalence of AGM among PCOS women residing in Northeastern region of Thailand than those in Bangkok may be secondary to the impact of food consumption behaviors which vary across the regions. Data from the Thai National Health Examination Survey IV observed that the carbohydrate-rich consumption i.e. sticky rice was more common in the North and Northeast of Thailand[21]. Several studies demonstrated the association of consumption of carbohydrate-rich food and an increased risk of developing abnormal glycemic status[22-24]. This may have led to higher prevalence of AGM in our study when compared to the study conducted in Bangkok albeit of the same age-group of PCOS population.

The present study demonstrated that PCOS women with AGM had significantly higher body weight, BMI, waist circumference, waist to hip ratio, blood pressure, and triglyceride level in comparison to those without AGM. These findings were in line with the previous studies in Thai PCOS women which also reported the association of these factors and an increased risk of AGM[14-17]. By mean of univariate analyses, women with age ≥ 30-year-old, BMI ≥ 25 kg/m^2, and waist circumference ≥ 80 cm were shown to have higher risk for AGM. Nevertheless, these variables were not statistically significant when adjusted with multiple logistic regression analyses. This was in line with findings previously report which demonstrated that age and BMI were not independent risk factors for AGM in PCOS patients[16]. In addition, a systematic review and meta-analysis assessing insulin resistance

in PCOS patients reported that a reduction in insulin sensitivity among PCOS women was independent of BMI and age[25]. These findings might highlight multifactorial involvement in glucose abnormality in PCOS patients[26].

This was the first study assessing the prevalence of AGM among PCOS women residing in the Northeast Thailand. Our study was able to denote some findings that appeared to be unique for our setting. The diagnostic criteria applied in our study was according to the update standard criteria. However, our study had some limitations. Firstly, the design of the present study was retrospective. Therefore, some informative data, particularly data regarding physical manifestations of insulin resistance i.e. acanthosis nigricans, androgenic status, details of exercise, and drinking behavior, were unavailable. Secondly, this study was undertaken in a single tertiary care hospital in the Northeast Thailand which limits an extrapolation of our findings to Thai PCOS women of different settings.

Conclusion

Abnormal glucose metabolism was highly prevalent among PCOS women residing in the Northeast Thailand with a rate of 34.6% in the present study. Pre-diabetes glycemic status including IFG and IGT was found in 30.9% of PCOS women. Approximately 5% of PCOS women in our study were diagnosed with T2DM. Patients' age and anthropometric measures were not independently associated with AGM.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Vaginal Bleeding Patterns in Women with Heart Disease Who Used Contraceptive Implants in Songklanagarind Hospital

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ABSTRACT

Objectives: The primary objective was to evaluate the vaginal bleeding patterns of women with heart disease who used contraceptive implants. The secondary objectives were to compare the results with healthy women (no underlying disease) and evaluate the rates and reasons for discontinuation.

Materials and Methods: A retrospective study was conducted at Songklanagarind Hospital from January 1, 2008 to December 31, 2017. The patients who used contraceptive implants were divided into two groups: women with heart disease and healthy women. The patterns of vaginal bleeding, discontinuation rate and reasons of discontinuation were recorded and compared.

Results: A total of 263 women who used contraceptive implants included 54 (20.5%) women with heart disease. Levonorgestrel implants were used most frequently (92.6%). The rate of abnormal vaginal bleeding was significantly higher in women with heart disease (94.4% vs 71.3%, $p < 0.01$). Abnormal vaginal bleeding patterns were irregular bleeding (33.3%), no bleeding (33.3%), and prolonged bleeding (14.8%). Women with heart disease (53.7%) who used anticoagulants had similar frequencies of overall abnormal vaginal bleeding patterns as the non-users of anticoagulants (95.8% vs 93.3%, $p = 1.00$). The discontinuation rates of contraceptive implants in women with heart disease were significantly lower than in healthy women (14.8% vs 29.7%, $p = 0.048$). The most common reason for discontinuation in women with heart disease was abnormal vaginal bleeding (62%).

Conclusion: The continuation rates of contraceptive implants in women with heart disease were high. The abnormal vaginal bleeding rate was 94.4%, especially irregular bleeding and no bleeding. Abnormal vaginal bleeding was the most common reason for discontinuation.

Keywords: Abnormal vaginal bleeding, contraceptive implants, discontinuation, heart disease.

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รูปแบบเลือดออกทางช่องคลอดของสตรีโรคหัวใจที่ใช้ยาฝังคุมกำเนิดในโรงพยาบาลสงขลานครินทร์

กล้า เจริญจิระตระกูล, สาธิต คลังสิน, ศรันญา วัฒนกำธรกุล, กรัณฑ์รัตน์ สุนทรพันธ์

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อศึกษารูปแบบของเลือดออกทางช่องคลอดของสตรีโรคหัวใจที่ฝังยาคุมกำเนิด เปรียบเทียบกับกลุ่มสตรีปกติ (ไม่มีโรคประจำตัว) ที่ฝังยาคุมกำเนิด วัตถุประสงค์รองเพื่อเปรียบเทียบอัตราการหยุดใช้ยาฝังคุมกำเนิดก่อนระยะเวลาจริง และเหตุผลที่หยุดใช้กับกลุ่มสตรีปกติ*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังในโรงพยาบาลสงขลานครินทร์ระหว่าง วันที่ 1 มกราคม 2551 ถึง 31 ธันวาคม 2560 ผู้ป่วยที่ใช้ยาฝังคุมกำเนิดถูกแบ่งเป็น 2 กลุ่มคือ สตรีโรคหัวใจและสตรีปกติ ทำการบันทึกและเปรียบเทียบรูปแบบเลือดออกทางช่องคลอด อัตราการหยุดใช้ยาก่อนเวลาจริง และเหตุผลที่หยุดใช้*

ผลการศึกษา: *สตรีทั้งหมด 263 คนที่ใช้ยาฝังคุมกำเนิด ประกอบด้วยสตรีโรคหัวใจ 54 คน (ร้อยละ 20.5) ส่วนใหญ่ร้อยละ 92.6 เลือกยาฝังคุมกำเนิดชนิด 5 ปี อัตราเลือดออกผิดปกติทางช่องคลอดของสตรีโรคหัวใจมากกว่ากลุ่มสตรีปกติอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 94.4 เปรียบเทียบกับร้อยละ 71.3)โดยรูปแบบของเลือดออกทางช่องคลอด เป็นเลือดออกกะปริดกะปรอยและไม่มีประจำเดือน ร้อยละ 33.3 ถัดมาเป็นเลือดออกเป็นระยะเวลานานร้อยละ 14.8 สตรีโรคหัวใจร้อยละ 53.7 ใช้ยาต้านการแข็งตัวของเลือดโดยมีรูปแบบเลือดออกผิดปกติทางช่องคลอดไม่แตกต่างจากกลุ่มที่ไม่ใช้ยาต้านการแข็งตัวของเลือด (ร้อยละ 95.8 เปรียบเทียบกับร้อยละ 93.3) อัตราการหยุดใช้ยาฝังคุมกำเนิดในสตรีโรคหัวใจต่ำกว่าในกลุ่มสตรีปกติอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 14.8 เปรียบเทียบกับร้อยละ 29.7) สตรีโรคหัวใจร้อยละ 62 หยุดใช้ยาฝังคุมกำเนิดเนื่องจากเลือดออกผิดปกติทางช่องคลอดมากที่สุด*

สรุป: *การใช้ยาฝังคุมกำเนิดในสตรีโรคหัวใจมีอัตราการใช้ต่อเนื่องสูง มีเลือดออกผิดปกติทางช่องคลอดหลังจากใช้ยาฝังคุมกำเนิดร้อยละ 94.4 ซึ่งส่วนใหญ่เป็น เลือดออกกะปริดกะปรอย และไม่มีประจำเดือน โดยอาการเลือดออกผิดปกติทางช่องคลอดเป็นสาเหตุสำคัญในการหยุดใช้ยาฝังคุมกำเนิดก่อนระยะเวลาจริง*

คำสำคัญ: *เลือดออกผิดปกติทางช่องคลอด, ยาฝังคุมกำเนิด, อัตราการหยุดใช้, โรคหัวใจ*

Introduction

A common cause of death in Thailand is heart disease, which consists of congenital heart disease including septal defect, valvular heart disease, and acquired heart diseases including rheumatic heart disease, myocarditis, and myocardial infarction. Although the mortality rate is decreasing[1], pregnancy causes increased blood volume and heart rates that lead to high morbidity and mortality rates during pregnancy, especially pregnancy with pulmonary hypertension that causes a mortality rate up to 30%[2]. In addition, 38% of all pregnancies with heart disease are categorized as high risk and 4% are contraindicated for pregnancy. Furthermore, the mortality rate is 1 in 100 compared with 7 in 100,000 in normal pregnancy[3]. In Songklanagarind Hospital, most pregnancies with heart disease are rheumatic heart disease. Morbidity and mortality during pregnancy were reported to be 24% and 3%, respectively[4]. Furthermore, some medications are teratogens such as warfarin that causes fetal warfarin syndrome and internal bleeding[5]. Therefore, contraception in women with heart disease is important.

A contraceptive method in women with heart disease requires many considerations such as long-acting, efficacy, and safety by medical eligibility criteria. In brief, categories 1 and 2 mean that a contraceptive method can be used in any circumstance or generally used and categories 3 and 4 mean a contraceptive method should not be provided[6].

Uncomplicated valvular heart disease has no limitations for contraception. Nevertheless, progestin therapy and an intrauterine device are suitable in complicated valvular heart disease, which includes pulmonary hypertension, atrial fibrillation, and subacute bacterial endocarditis[6]. Progestin only pills, contraceptive implants, and intrauterine device are suitable for patients with ischemic heart disease[7]. When considering the efficacy, contraceptive implants and intrauterine devices are suitable.

Three types of contraceptive implants are available: Implanon®, Jadelle®, and Levoplant®. In Songklanagarind Hospital we use Implanon® and Jadelle®. Implanon® is a single-rod implant that contains 68 mg of etonogestrel and Jadelle® is a double-rod implant that contains 150 mg of levonorgestrel. Both devices inhibit ovulation and produce a thick cervical mucus and have the highest efficacy of 1 pregnancy in 1,000 users[6]. However, the common side effect is abnormal vaginal bleeding as a consequence of endometrial thinning[8].

From a literature review, no explanation has been published on whether or not heart disease changes the bleeding patterns in women who use contraceptive implants. However, some women with heart disease in this study needed an anticoagulant. Previous studies evaluated bleeding patterns in women on warfarin therapy while using levonorgestrel containing contraceptives. They found drug interaction between warfarin and the levonorgestrel-containing contraceptives. They concluded that progestin binds to the F1-S variant of human α1-acid glycoprotein which is the protein transport of warfarin[9, 10].

Recently, no study has evaluated vaginal bleeding patterns in the specific group of women with heart disease who use only contraceptive implants. Therefore, our primary objective was to evaluate the vaginal bleeding patterns of women with heart disease who used contraceptive implants. The secondary objectives were to compare the results with healthy women who used contraceptive implants and evaluate discontinuation rates and reasons of discontinuation.

Materials and Methods

A retrospective study was conducted after the protocol approval by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC.61-246-12-4). The medical records were reviewed of all patients from the database of the Unit of Family Planning, Department of Obstetrics and Gynecology at Songklanagarind Hospital between 1 January 2008 and 31 December 2017. The exclusion criteria were incomplete data (i.e. no data of vaginal bleeding patterns or reasons for discontinuation) or lost to follow-up (i.e. no follow-up before implant removal or incomplete contractive implant use), women with

underlying diseases other than heart disease, and women with abnormal menstruation before using a contraceptive implant. In our institute, guidance for choices of contraception in women with heart disease follows a global handbook from World Health Organization (WHO)[6]. In women with uncomplicated valvular heart disease and WHO class I/II, the choice of contraception depends on fertility desire, and the needed duration of contraception. Women with complicated valvular heart disease and WHO class III/IV are counseled the irreversible contraceptive methods. If they refuse an irreversible contraceptive method, long-acting reversible methods are offered based on the medical eligibility criteria.

Patients using contraceptive implants were divided into two groups: women with heart disease and women with a healthy status (no medical condition). The demographic data, pattern of abnormal bleeding, discontinuation rate, and reasons of discontinuation were recorded and compared between the two groups. The medical records of all eligible patients were retrospectively reviewed by the investigator.

Two types of contraceptive implants were available for the study: etonogestrel containing contraceptive implant (Implanon®, Merck & Co., Inc, Whitehouse Station NJ, USA) and levonorgestrel containing contraceptive implants (Jadelle®, Bayer Healthcare, Berlin, Germany).

Abnormal vaginal bleeding was defined as prolonged bleeding, irregular bleeding, lighter bleeding, infrequent bleeding, and no bleeding according to the International Federation of Gynecology and Obstetrics (FIGO) recommendation of 2011[11] and the WHO family planning guidelines of 2018[6] (Table 1).

Table 1. Definition of abnormal vaginal bleeding patterns[6, 11].

Abnormal vaginal bleeding patterns	Definition
No bleeding	No days of bleeding/spotting entered throughout the reference period
Lighter bleeding	Lighter bleeding and fewer days of bleeding
Prolonged bleeding	≥ 10 days in one episode
Infrequent bleeding	< 2 episodes in one 90-day reference period
Irregular bleeding	A range of varying lengths of bleeding-free interval > 17 days within one 90-day reference period

Data are presented as mean ± standard deviation or n (%). BMI: body mass index

In our institute, when a patient needs removal of a contraceptive implant because of side effects, the attending physician advises, reassures, and manages the side effects. If the patients maintain their desire to discontinue using the implant, the other contraceptive methods are offered.

The data were collected using EpiData Version 3.1 and used the R-program for the statistical analysis. Descriptive statistics were used. Univariate analysis was done to compare the difference of vaginal bleeding from a contraceptive implant between women with heart disease and normal women using the chi square or Fisher's exact test for nominal variables and the student's t-test or Wilcoxon's rank sum test for continuous variables. A multiple logistic regression analysis was performed to identify independent risk factors. Statistical significance was set at $p < 0.05$.

Results

A total of 327 women used contraceptive implants that were prescribed at the Unit of Family Planning during the study period. Sixty-four women were excluded because of abnormal vaginal bleeding before application of an implant and underlying diseases such as diabetes, hypertension, autoimmune disease and human immunodeficiency virus (HIV) (Fig. 1). Finally, 263 women were enrolled in the study that included 54 (20.5%) women with heart disease and 209 (79.5%) healthy women.

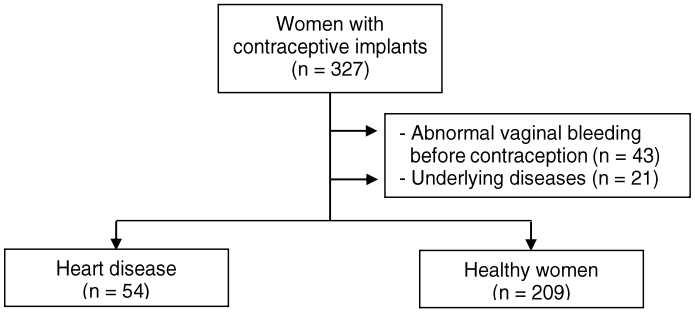

Fig. 1. Patient Flow Chart.

The demographic data of women with heart disease and healthy women who used contraceptive implants are shown in Table 2. Women with heart disease had a significantly higher nulliparity rate (32.8% vs 15.5%, $p < 0.05$) and lower body mass index (21.4 vs 22.4 kg/m^2, $p < 0.05$).

The median (interquartile range) age of women with heart disease was 28 (25, 34.8) years. Thirty-eight patients had acquired heart disease. According to the modified WHO classification of maternal cardiovascular risk, the most common was WHO class III (48.1%) followed by WHO class IV (27.7%), which has a high mortality rate during pregnancy. The 54 women were categorized according to the modified WHO classification: class I included repaired ventricular septal defect[1] and mild pulmonary stenosis/tricuspid regurgitation[2]; class II included atrial/ventricular septal defect (7) and repaired tetralogy of Fallot[3]; class III included mechanical valve[22], moderate mitral stenosis[1], and tetralogy of Fallot[3]; and class IV included pulmonary arterial hypertension[10], severe mitral valve stenosis[3], and dilated cardiomyopathy[2]. According to the New York Heart Association Functional Classification, most women were class I (54.4%) and class II (43.9%) at the time of implant insertion.

Table 2. Demographic data of women with heart disease and healthy women who used contraceptive implants.

Characteristics	Women with heart disease (n = 54)	Healthy women (n = 209)
Age (years), median (IQR)	28 (25, 34.8)	30 (24, 36)
Nulliparity	15 (28.8)*	24 (15.5)
BMI (kg/m^2), median (IQR)	21.4 (19.4, 23.8)*	22.4 (20.7, 24.9)
Type of contraceptive implants		
Etonogestrel	4 (7.4)*	87 (41.6)
Levonorgestrel	50 (92.6)*	122 (58.4)
Type of heart disease		
Congenital	20 (37)	
Acquired	34 (63)	
WHO classification		
Class I	3 (5.5)	
Class II	10 (18.5)	
Class III	26 (48.1)	
Class IV	15 (27.7)	
Anticoagulant users	29 (53.7)	

Data are presented as n (%) unless otherwise indicated. IQR: interquartile range, BMI: Body mass index, WHO: World Health Organization. *$p < 0.05$

Most women with heart disease chose levonorgestrel (92.6%), while 7.4% chose etonogestrel containing contraceptive implants. The percentage of women who used the levonorgestrel implant was greater than the group of healthy women (92.6% vs 65.4%, $p < 0.05$) (Table 2).

After using contraceptive implants, 51 (94.4%) women with heart disease had a significantly higher overall rate of abnormal vaginal bleeding compared with the healthy women (149/209, 71.3%). Abnormal vaginal bleeding patterns in women with heart disease were irregular bleeding (33%), no bleeding (33%), prolonged bleeding (14.8%), infrequent bleeding (13%), and lighter bleeding (13%) (Fig. 2). Some patients had more than one abnormal vaginal pattern. However, the timing of having the episode of any abnormal bleeding pattern was similar between the two groups: 1-8 months in women with heart disease and 1-7 months in healthy women.

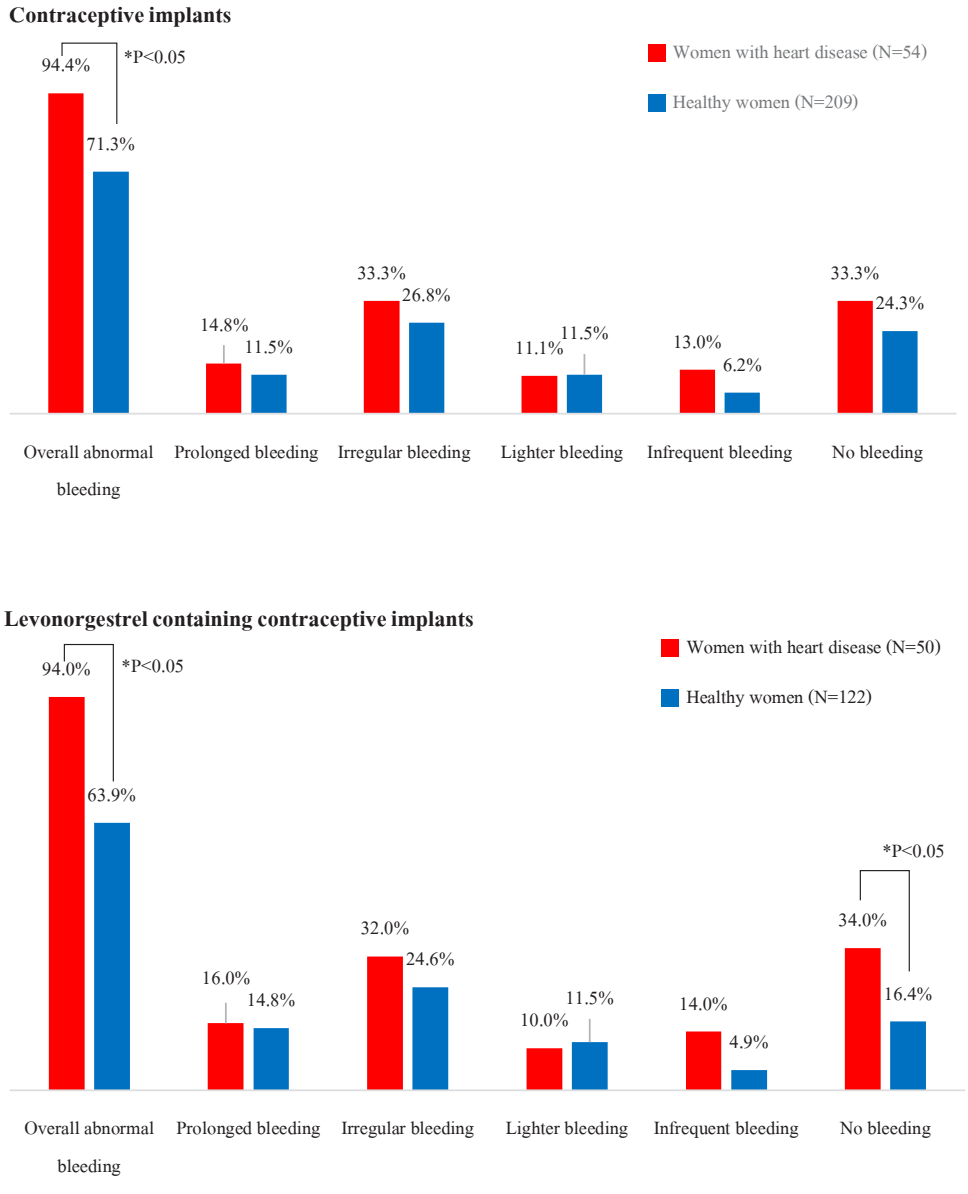

Fig. 2. Comparison of frequency of abnormal vaginal bleeding patterns between women with heart disease and healthy women who used contraceptive implants

When focusing on women who used only levonorgestrel containing contraceptive implants, women with heart disease had a significantly higher overall rate of abnormal vaginal bleeding compared with the healthy women (94% vs 63.9%, $p < 0.05$) (Fig. 2).

Anticoagulants were used in 29/54 (53.7%) women with heart disease who used contraceptive implants. When we compared vaginal bleeding patterns in women with heart disease who used and those who did not use anticoagulant medications, we found no significant differences (95.8% vs 93.3%, $p = 1.00$) (Table 3). Among the 29 anticoagulant users, the mean international normalized ratio (INR) level before using a contraceptive implant was 2.5 ± 0.9, while the mean INR level was 2.2 ± 0.7 after insertion of an implant.

The discontinuation rates of contraceptive implants in women with heart disease were significantly lower than in the healthy women (14.8% vs 29.7%, $p = 0.048$). The reasons for discontinuation in the women with heart disease were abnormal vaginal bleeding (62.5%) and personal reasons (37.5%), while the reasons for discontinuation in the healthy women were personal reasons (53.2%) and abnormal vaginal bleeding (25.8%). The details of personal reasons are shown in Table 4.

Table 3. Comparison of frequencies of abnormal vaginal bleeding patterns of women with heart disease and healthy women (n = 263) between anticoagulant and non-anticoagulant users.

Abnormal vaginal bleeding patterns	Anticoagulant users (n = 24)	Non-anticoagulant users (n = 30)	p value
Overall abnormal bleeding	23 (95.8)	28 (93.3)	1.000
Heavy bleeding			
Prolonged bleeding	6 (25)	2 (6.7)	0.12
Irregular bleeding	8 (33.3)	10 (33.3)	1
Non-heavy bleeding			
Lighter bleeding	2 (8.3)	4 (13.3)	0.682
Infrequent bleeding	4 (16.7)	3 (10)	0.687
No bleeding	7 (29.2)	11 (36.7)	0.771

Data are presented as n (%).

Table 4. Comparison of discontinuation rates and reasons of discontinuation between women with heart disease and healthy women who used contraceptive implants.

	Women with heart disease (n = 54)	Healthy women (n = 209)
Discontinued	8 (14.8)*	62 (29.7)
Reasons of discontinuation		
Abnormal vaginal bleeding	5 (62.5)	16 (25.8)
Personal reasons	3 (37.5)	33 (53.2)
Fertility needed	3 (37.5)	22 (35.5)
Divorce	0	3 (4.8)
Switch to other method	0	8 (12.9)
Increased body weight	0	7 (11.3)
Acne	0	3 (4.8)
Headache	0	3 (4.8)

Data are presented as n (%). *$p < 0.05$

Discussion

Songklanagarind Hospital is a super-tertiary care university hospital in southern Thailand. Therefore, most cases of pregnancy in the region with heart disease are referred to this hospital. Based on a study by Suwanrath et al[4], pregnancy was contraindicated in one out of four of patients with heart disease and the occurrence of maternal cardiovascular events increased significantly with a higher WHO classification. A highly effective contraceptive method with a long-acting mechanism is the preferred choice, especially when considering contraceptive implants.

The purpose of this retrospective study, which evaluated the vaginal bleeding patterns in women with heart disease compared with healthy women, was to inform the women regarding bleeding patterns and prevent them from implant discontinuation. Most women with heart disease (92.6%) used levonorgestrel containing contraceptive implants because of the prolonged duration for contraception. Based on the WHO classification, most of them were class III (48.1%) and class IV (27.7%). These results were similar to a previous study that used a long-acting reversible method in high severity cases according to the WHO classification because these groups were contraindicated for pregnancy and the long-acting method was suitable for them[12].

In this present study, abnormal vaginal bleeding from contraceptive implants was significantly higher in women with heart disease (94.4% vs 71.3%, $p < 0.05$). Most women used levonorgestrel containing contraceptive implants. Therefore, a subgroup analysis was conducted to compare bleeding between women with heart disease and healthy women who used only levonorgestrel containing contraceptive implants. We found that the incidence of abnormal vaginal bleeding was still significantly higher in women with heart disease. Based on previous studies, we suspected this result was possibly explained by drug interaction between warfarin and levonorgestrel. Zingone et al described the mechanisms of interaction that were: i) inhibition or induction of cytochrome P450 enzymes, ii) alteration of the coagulation cascade by hormonal contraceptives, and iii) protein binding displacement[9]. A study by Laine et al found that etonogestrel and levonorgestrel inhibited CYP2C9, 2C19, and 3A4[13].

A previous study reported that etonogestrel containing contraceptive implants affected the coagulation cascade, especially factors II, X, XI, and protein C but did not affect the prothrombin time[14]. Levonorgestrel might affect factor IX by displacing the protein binding of warfarin along with an elevated INR[10, 15]. We considered that an abnormal INR level might have an effect on bleeding patterns. However, a subgroup analysis in women with heart disease who used anticoagulant medications were found to have no increased INR levels after contraceptive implant insertion. Even though all anticoagulant users had normal INR values, no data were available on anticoagulant dosage changes and some data of the INR were missing during the use of contraceptive implants. In our institute, the cardiologists and cardiovascular thoracic surgeons have a target INR range of 2.0-3.5. However, when we conducted a subgroup analysis in women with heart disease to compare women who used anticoagulant medications with those who did not use anticoagulants, we found no significant difference of abnormal vaginal bleeding patterns. Therefore, we could not conclude that anticoagulants had any effect on vaginal bleeding patterns. This was possibly due to the small sample size.

Based on the comparison of patterns of vaginal bleeding between women with heart disease and healthy women who used contraceptive implants, no significant differences between the two groups were observed. In women with heart disease, most bleeding patterns were irregular bleeding (33%) and no bleeding (33%). Due to the lack of data in women with heart disease, we compared the present study with a previous study in a normal population. We found that the most common pattern was also irregular bleeding (48.5%)[16].

Overall, the continuation rate in women with heart disease was significantly higher than in the healthy group (85.2% vs 70.3%, $p = 0.048$). The continuation

rate in women with heart disease in the present study was higher compared with a previous study that reported 52% in a normal population[16]. The high continuation rates in contraceptive implants revealed that women with heart disease realized their heart disease was a contraindication for pregnancy as most of these women were WHO class III and class IV. They were possibly aware of the benefits of this method and were knowledgeable of the complications if they got pregnant. Abnormal vaginal bleeding was the most common reason to discontinue a contraceptive implant in women with heart disease (62.5%) which was similar to a previous study (54%)[16]. However, in healthy women, personal reasons were the most common for discontinuation (53.2%). Only one previous study by Bahamondes et al also reported personal reasons as the most common (16.4%)[16]. An in-depth analysis found that the personal reasons included fertility desire, divorce, and switch to another method.

This study has some strengths and limitations. One strength was this study provided the first descriptive data in women with heart disease using contraceptive implants. The important point in these patients is how to continue the method to prevent unintended pregnancy. The data on abnormal vaginal bleeding patterns and the reasons of discontinuation can assist health care providers with more confidence in prescribing contraceptive implants in women with heart disease. The retrospective nature of this study was a limitation. Some specific data could not be collected, especially changes in the dosage of an anticoagulant medication, duration of use, and the level of coagulation. However, the medical records were collected from a computer-based hospital information system.

Although the discontinuation rate was low in the present study, abnormal vaginal bleeding was still the most common reason to discontinue a contraceptive implant in women with heart disease. In-depth counseling is preferred in these patients to perceive the benefits of this method beyond the side effects.

Conclusion

The continuation rates of contraceptive implants in women with heart disease were high (85.2%) even though abnormal vaginal bleeding from contraceptive implants in women with heart disease was found to be in 94.4%. The two most common patterns of abnormal vaginal bleeding were irregular bleeding and no bleeding. These two reasons were the most common reasons to discontinue using a contraceptive implant.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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