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Thai Journal of Obstetrics and Gynaecology

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Type of Paper: Special (invited) article, Original article, Case report
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EDITORIAL

This third issue of Thai Journal of Obstetrics and Gynaecology 2022 contains many interesting articles. One special article is "Fertility Preservation Strategies in Gynecologic Cancers". The authors reviewed types of gynecologic cancers that could be performed fertility sparing.

Royal Thai College of Obstetricians and Gynaecologists (RTCOG) mid year meeting 2022 was held during 26-29 April 2022 at Dusit Thani Hua Hin Hotel, Phetchaburi, Thailand. The theme of this meeting was "Talking OB-GYN". The meeting was successful with 1,075 participants.

Due to the high number of COVID-19 infected cases, all RTCOG members please keep yourself and others safe from COVID-19: social distancing, maintain at least a 1-metre distance, make wearing a mask a normal part, regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water, avoid touching your eyes, nose and mouth, cover your mouth and nose with your bent elbow or tissue when you cough or sneeze, and avoid crowded or indoor settings.

Wish all RTCOG members and families safe from COVID-19.

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

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SPECIAL ARTICLE

Fertility Preservation Strategies in Gynecologic Cancers

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ABSTRACT

The incidence of most gynecologic malignancies significantly reaches their peaks after the age of 50, a substantial number of women encounter the diagnosis of gynecologic cancer during their reproductive year. Thus, fertility preservation has an important role in good quality of life in adolescents and young adults. The gynecologic oncologists should thoroughly discuss the potentiate infertility with all patients and refer them to reproductive specialists as earliest as possible to broaden the fertility preservation options and reduce decisional regret. There are roles of fertility preservation treatment in appropriately selected patients such as early stage cervical cancer (IA1-IB1), early stage of endometrial carcinoma with well-differentiated endometrioid subtype, and some subtypes of ovarian cancer (epithelium ovarian cancer stage IA, epithelium ovarian cancer unilateral stage IC, malignant ovarian germ cell tumor, sex-cord stromal tumor, borderline ovarian tumor) which the fertility preserving procedure yields the optimal oncologic outcomes and acceptable obstetrics result. Patients should be insistently informed that the fertility sparing treatment is not the standard of care and accepted possibilities of impaired survival. The doctors should emphasize comprehensive surveillance and a complete surgical staging following family completion must be achieved.

Keywords: fertility sparing, gynecology cancer, fertility preservation.

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Although the incidences of most gynecologic malignancies significantly reach their peaks after the age of 50, a substantial number of women encounter with the diagnosis of gynecologic cancer during their reproductive years. In the United States, out of the 113,520 women estimated to be diagnosed of female genital tract cancer in 2020, 21% was younger than 40 years[1]. In combination with the increasing sociodemographic transition towards women having their first childbirth beyond age 35, reproductive aging, and gonadotoxic treatments, fertility issues have become more frequent and complicated in women with cancer. Accordingly, the ultimate goals of oncologic treatment have expanded from the more survival to the

improved quality of life after surviving cancer[2]. Preservation of fertility play an important role of good quality of life in adolescents and young adults[3]. The objectives of this clinical review were to summarize and update in fertility preservation approaches.

Bases on the guidelines from the American Society of Clinical Oncology and the American Society for Reproductive Medicine, the oncologists should thoroughly discuss the potentiate infertility with all of the patients and refer them to the reproductive specialists as earliest as possible[4, 5]; as the prompt referrals broaden the fertility preservation options. The patients receiving pretreatment fertility preservation counselling experience less decisional regret in spite of their decisions to forego fertility preservation treatments. However, even with these recommendations, the referral rates to the reproductive specialists remain low[6, 7]. The contents should cover the variations in types of cancer, available time to the onset of the treatment, extents of the surgery, types and dosages of chemotherapy, types and dosages of radiation and the risk of sterility with the given treatments.

Fertility preservation strategies in gynecologic cancers

Female fertility is at risk following surgery, chemotherapy, or radiotherapy treatment for cancer(8). Ovarian damage from drugs is type and dose dependent and is related to the patients' age at the time of the treatment, while the progressively smaller doses can also cause ovarian failure as the patients' age. Total body, abdominal, or pelvic irradiation probably leads to ovarian and uterine damage, based on the radiation dose, fractionation schedule, and age at receiving the treatment[9]. An increased serum follicle-stimulating hormone (FSH) level is commonly used to indicate ovarian damage and failure. However, anti-mullerian hormone (AMH) and antral follicle count (AFC) are now comprehensively applied as other biochemical indicators of ovarian aging. For female cancer patient, fertility should be evaluated on a basis of a complete history, a thorough physical examination, laboratories and pelvic ultrasound[10]. Nevertheless, the most significant predictor of the reproductive potential and live birth rates is the patient's age. The recommended steps to approach each patient are as follows.

Comprehensively taken the medical, gynecologic, and surgical history

- Detailed menstrual history (menarche, cycle interval and length, and presence of ovulation)
- Obstetric history (gravidity, parity, time to previous pregnancies, and mode of delivery)
- History of prior fertility testing or treatment
- Partner reproductive history

Physical examination

- Vital signs, body mass index
- Thyroid gland
- Breast
- Pelvic examinations (uterine size, shape, position, adnexal masses, or tenderness)

Transvaginal ultrasound examination

- Uterine characteristics
- AFC (total number of small follicles that measure between 2-10 mm. in diameter on an early follicular phase), ovarian volume

Biochemical measures of ovarian reserve

- Serum FSH, estradiol, and inhibin B (measured in the early follicular phase)
- AMH

Fertility preservation options

1. Embryo cryopreservation

In the past, embryo cryopreservation was the sole alternative for the female cancer patients wishing for fertility preservation. Its limitation is the requirement of a specified partner contributing to fertilization the sperm with eggs.

2. Oocyte cryopreservation

The patients without a partner, refusing donor sperm or embryo cryopreservation may opt for ovarian stimulation and oocyte retrieval which freeze the eggs to be subsequently thawed. Lately, many institutes increase the pregnancy rates from using cryopreserved and warmed oocyte using cryoprotectants and cryotools

along with rapid cryopreservation technique (vitrification) and fertilization with intracytoplasmic sperm injection (ICSI)[11, 12]. Based on the available data, the Practice Committee of the Reproductive Medicine, recommended ovarian cryopreservation for the women, with high potential of ovarian failure, who are not candidate for embryo cryopreservation[13].

3. Ovarian tissue cryopreservation

At the moment, it is the only feasible option for prepubertal girls and the patients who must immediately start their chemotherapy or radiation treatment with inevitable delay[14]. However, the ischemic damage to the tissue pending the transplant and revascularization, not to mention the theoretical exposure to occult malignant tumor cells. If these obstacles are overcome, ovarian tissue preservation can facilitate the prompt treatment, avoidance hormonal use to stimulate the ovaries in the patients who can appropriately undergo laparoscopic ovarian biopsy or oophorectomy. Ovarian function usually returns within 2–8 months post-transplant and remains up to 7 years[5]. There are some controversies; still, a recent meta-analysis in 2017 reported as high as 37.7% cumulative live birth rate following ovarian tissue cryopreservation[15].

4. Ovarian transposition

If the patients require pelvic irradiation for their cancer, ovarian transposition (oophoropexy) is among other choice to be considered. Unfortunately, due to undeniable radiation scatter, ovaries may not completely survive and the thoroughly informed of the possible failure, from the systematic review, 67% of the cervical cancer patients undergoing ovarian transposition have their ovarian function preserved, ranging from 16.6-100%[16].

5. Ovarian suppression with gonadotropin releasing hormone (GnRH)

Based on a study in breast cancer patients treated with chemotherapy, GnRH analogs may partially reduce chemotherapy-induced primary ovarian insufficiency in the patients under age 40. In contrast, a randomized trial reported no benefit in ovarian reserve protection, indicated by AMH and FSH as surrogate markers[17, 18]. There is still insufficient long-term data on the return of menstrual function, ovulation, and pregnancy rates following chemotherapy in patients receiving GnRH analogs and further studies are needed to comprehensively determine the advantages of this medication in term of fertility and/ or endocrine function preservation[5].

Fertility sparing by cancer site

1. Cervical cancer

Cervical cancer is commonly diagnosed in reproductive age women, as high as 37% of the new cases are encountered in women below 45[19]. The following criteria should be met in the fertility sparing surgical candidates:

- Histologic type: squamous cell carcinoma, adenocarcinoma or adenosquamous histology
- Tumor size: lesion less than or equal to 2 cm
- Other risk factors: no deep stromal invasion
- No evidence of lymph node involvement
- No distant metastatic disease

According to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging of cervical cancer, the clinically early-stage patient treatments are as follows[20].

1. Stage 1A1 with no lymphovascular invasion (LVSI): Cervical conization with negative margin at least 3 mm preferably a non-fragment specimen along with negative tissue from endocervical curettage. If the margin was positive, re-procedure or trachelectomy is recommended. The risk of recurrence after conization in patients with stage IA1 disease, with no LVSI, negative endocervical curetting after excision, and negative surgical margins was less than 0.5%[21].

2. Stage 1A1 with positive LVSI, stage 1A2: Radical trachelectomy with pelvic lymphadenectomy (considering sentinel lymph nodes (SLN) mapping in case of tumor size less than or equal to 2 cm) is recommended. Cervical conization with negative margin, a non-fragment specimen and negative tissue from endocervical curettage with pelvic lymphadenectomy can also be an option (considering SLN mapping in case of tumor size less than or equal to 2 cm). However,

in the patients with positive LVSI, the risk of recurrence may increase up to 9%, necessitating the pelvic lymph node dissection with the recommended SLN mapping.

3. Stage 1B1: Radical trachelectomy with pelvic lymphadenectomy (considering SLN mapping in case of tumor size less than or equal to 2 cm) with or without paraaortic lymphadenectomy.

4. Stage 1B2 (in selected cases): From a systematic review, in the advanced cervical cancer with tumor size 2-4 cm, neoadjuvant chemotherapy with platinum-based regimen followed by fertility sparing surgery feasibly preserved the patients' fertility[22]. Nonetheless, the data is limited, and the high risk of recurrence (6%) raises the concerns in terms of the oncological safety. These options should cautiously be offered to the highly selected patients.

Radical trachelectomy with pelvic lymphadenectomy can be accomplished with the abdominal (AT), vaginal (VT) or minimally invasive approached (laparoscopy or robotic surgery). Nonetheless, cervical excisional procedures are notably associated with the substantially increased obstetric complications, such as preterm delivery and prematurity, mainly as a consequence of the loss of cervical anatomical support and physiological function. In addition, cervical stenosis is highly contributed to complicated procedures. Because the infertility rates following the procedures range from 14%–41%, assisted reproductive technologies (ART) are imperative to achieve pregnancy[23, 24].

A systematic review, focusing on the reproductive and oncologic outcome after fertility-sparing surgery for the early-stage cervical cancer endorsed this option as an alternative to the conventional radical hysterectomy in women desiring fertility preservation. The mean clinical pregnancy rate of patients who tried to conceive was 55.4%. The mean live birth rate was 67.9%, 20 percent of which required ART. Regarding the oncological issues, the mean recurrence rate was 3.2% and the cancer death rate was 0.6%, based on the median follow-up period of 39.7 months[25].

Before the fertility-sparing surgery for early-stage cervical cancer, the patients must comprehensively be informed of all intraoperative and postoperative findings that can possibly lead to the loss of fertility. Intraoperatively, if adequate margins and/or positive lymph nodes are encountered, the scheduled fertility sparing procedure will be fortified. Despite completion of the fertility sparing surgery, post procedurally, a small number of the patients will eventually need adjuvant chemoradiation based on their final pathological report, affecting the preserved uterus and diminish the chance to successful pregnancy[24].

2. Endometrial cancer (EC)

The overall incidence of EC has rapidly increased, especially in the proven under 40, who are unsurprisingly nulliparous and consequently, desire to maintain childbearing ability. Fortunately, young women are usually diagnosed in the early stages and low grade, possessing good prognosis. Besides the counselling on the standard treatment for EC, total hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic washing, with or without lymphadenectomy[26], for fertility-sparing consideration, the patients must be practically assessed potentiality of spontaneous conception in the context of such as chronic anovulation or polycystic ovarian syndrome, the feasibility and total cost of ART[27, 28]. Before considering fertility preservation, the following criteria should be fulfilled[29].

- Young women of child-bearing age (preferably under 40 years) diagnosed with endometrial cancer, stage IA.
- Well-differentiated tumors with < 50% myometrial invasion assessed by magnetic resonance imaging (MRI).
- No evidence of pathological lymph nodes (the risk of pelvic and paraaortic lymph node involvement is 4.7 and 1.7%, respectively)[30].
- No evidence of synchronous or metachronous ovarian tumors (adnexa involvement and ovarian coexisting neoplasm is 6 and 19%, respectively)[30].
- No family history or hereditary cancer syndromes, as evidenced by mutation testing primarily for Lynch syndrome by immunohistochemical staining of the tumor specimens for mismatch repair (MMR) proteins. The MMR deficiency in patient with endometrial cancer is linked with an increased rate of synchronous

or metachronous ovarian tumors (10-29%) and significantly worse progression-free survival (48.6% vs 83.3%), as well as overall survival (56.5% vs 90.0%)[31-33].

Even though the initial diagnosis is made by an office endometrial biopsy, dilation and curettage should still be performed for the sake of better determining cancer grade[34]. Hysteroscopic biopsy is also proposed because of the more accurate final pathologic examination in comparison with dilatation and curettage[35, 36]. Despite the tentatively higher rate of peritoneal cytology, the survival is not evidently impacted[37]. MRI examination is the best investigational tool to evaluate the extent of myometrium infiltration, with a sensitivity and a specificity of 74%(38). Alternatively, expert transvaginal ultrasound examination can be applied[39].

Hormonal treatment

At the present time, the regimens of hormonal therapy in fertility preserving treatment are not standardized, however, based on the well conducted studies, the recommendations are oral form alone or in combination with intrauterine system with or without GnRH analogs. Over more, the successful treatment depends on hormone receptor expression on cancer cells, with the response rate from 26% to 89% in estrogen and progesterone receptor positive tumors and as low as 8-17% in the receptor negative group[40, 41]. The advised management are as below.

1. Medroxyprogesterone acetate (MPA): 400–600 mg daily
2. Megestrol acetate: 160–320 mg daily
3. Intrauterine device (IUD): 20, 52 mg daily levonorgestrel (LNG) (combination with oral progestins with or without GnRH analogs)
4. GnRH analogs

In two systematic reviews recruiting patients with both atypical hyperplasia and stage I endometrial cancer given varies progestin-containing regimens, hormonal therapy yielded an acceptable complete response rate of 71–78%, with approximately one third of patients achieving pregnancy[42, 43]. Interestingly, this affected more evidently in, comparing with carcinoma (66% vs 48%). Unfortunately, upon follow-up of them with initial responses, 23% with hyperplasia and 35% with carcinoma encountered a recurrence. A meta-analysis including 1,038 women reported the higher pooled response rates in women using both the LNG-IUD and oral progestins, in comparison with LNG-IUD and oral progestins alone (87% vs 76% and 71%, respectively)[43]. In addition, there are other non-hormonal treatment options.

1. Hysteroscopic resection

The surgical technique pointing out a lesion which has a suspicious malignant characteristic was first reported by Mazzon et al[44]. From a meta-analysis in 2010, in combination with hormonal therapies, hysteroscopic resection was validated as an auspicious treatment with a regression rate of 100%; whereas the hormonal therapy alone and surgery alone achieved 49.6 and 75% regression rate, respectively[45]. Nonetheless, intrauterine adhesion possibly undeniably occurs[46].

2. Weight loss

Presently, the correlation between weight loss and risk reduction of recurrence increased survival in endometrial carcinoma patients lacks of high quality evidence, especially in terms of fertility sparing treatment[39].

3. Metformin

Metformin expresses the antineoplastic activity by stimulating multiple signaling pathways in cell metabolism[47] possibly interferes the estrogen mediated endometrial proliferation[48]. Metformin administration along with tentatively associates with an improved overall survival in patients with endometrial carcinoma and a reduced cancer relapse risk.

The appropriate follow-up schedule for women after hormonal treatment option for fertility sparing patients with endometrial cancer is not established. Based on the risk of endometrial cancer progression, office endometrial biopsy (possibly performed with an IUD in place) is recommended in some institutional protocols every 3 - 6 months, until two consecutive negative biopsies are noted, if a complete response is proved, conception should be authorized. Upon complete childbearing, definitive hysterectomy should be encouraged, owing to the evident long-term

recurrences[49].

When definitive surgical staging is indicated, ovarian preservation is justified in patients with early-stage, low-grade tumors with grossly normal appearing ovaries intraoperatively. A large database study confirmed the safety of ovarian preservation in women under age 50 at the time of endometrial cancer surgery for the benefits of maintain function which is related to the decreased risk of death from cardiovascular disease and improved overall survival[50, 51].

3. Ovarian cancer

Ovarian cancer is mostly diagnosed among postmenopausal women. Unfortunately, around 12% of the patients suffer with this disease during their reproductive years[52]. Surgical staging which consists of hysterectomy, BSO, omentectomy, peritoneal washings, and pelvic and para-aortic lymphadenectomy is the standard treatment. The pathology of the tumor is normally not obtained until after the operation, leading to more diagnostic challenges than endometrial and cervical cancer. Therefore, any patients with an adnexal mass should undergo a thorough preoperative evaluation, comprising imaging studies and tumor markers. Intraoperative decision-making is critical and relies on an operative findings and frozen section. In addition, a patient must understand that frozen section pathology may be different from the final pathology and a two-step procedure is inevitable in some conditions[53, 54].

Currently, the consensus on the criteria for conservative approach is not settled but according to current evidence and recommended guideline, fertility sparing surgery can be opted subjecting to the histology and disease stage[55]. A fertility sparing surgery probably consists of an ovarian cystectomy or unilateral salpingo-oophorectomy (USO), omentectomy, peritoneal washings, pelvic and paraaortic lymphadenectomy, and peritoneal biopsies, preserving of the uterus and contralateral ovary. The routine biopsy of a normal appearing contralateral ovary is not recommended. The diverse extent of the necessary steps of the procedure is decided by the ovarian tumor histology.

3.1. Epithelium ovarian cancer

A large cohort study based on the US National Cancer Database revealed no association between fertility sparing surgery in stage IA or unilateral stage IC epithelial ovarian cancer and an increased risk of death, comparing to conventional surgery. However, the number of patients with high-risk histology were comparatively low[56], the safety of fertility sparing surgery in patients with high-risk features, such as stage IC disease or other high grade histology raised some concerns[57, 58]. The patients with stage IC epithelial ovarian cancer or other high-risk features should be conscientiously informed of the limited oncologic safety data. The recommended procedures are USO and comprehensive surgical staging (peritoneal sampling, omentectomy, pelvic and para-aortic lymphadenectomy) if the lesion is encapsulated, well differentiated and unilateral disease, with no extra ovarian metastasis, adhesion or ascites[59]. The previous studied of the reproductive outcome demonstrated the average pregnancy rate of 36% with 82% live birth[41].

3.2. Borderline ovarian tumors (BOT)

Accounting for 10% to 20% of the overall ovarian epithelial tumors, the incidence of BOT is 1.8 to 4.8 per 100,000 women per year[60], which is rising, especially in the patients in childbearing age[61, 62]. In the women with fertility desire, the surgical management is limited to USO with complete surgical staging (abdominal cavity exploration, peritoneal washing, infra-colic omentectomy, multiple peritoneum biopsies)[59], on condition that the disease is confined to a single ovary[63]. Ovarian cystectomy is acceptable, providing that the patients must realize that the recurrence rates are greater than 30%. If there is bilateral ovarian involvement and complete resection can be accomplished, ovarian cystectomy is the treatment of choice[64]. Based on the 2020 prospective study, the overall recurrence rate was 1.1% in FIGO stage I and 25.5% in FIGO stage III-IV. The relapse of all BOT was 13.7%. The significant risk factors for recurrent disease are FIGO stage III-IV and fertility sparing surgery[65].

3.3 Sex-cord stromal tumor (SCSTs)

SCSTs was diagnosed in 7% of the ovarian cancer patients, and the mean age at diagnosis is 50 years. However, Sertoli Leydig tumor or juvenile-type granulosa cell tumor are often encountered between ages 10 years and 30 years, who may be candidates for fertility preservation[66]. Approximately 57% of the malignant SCSTs are stage 1A, with a promising prognosis. The National Comprehensive Cancer Network (NCCN) guidelines[63] suggest the fertility sparing option, which includes USO and comprehensive surgical staging (the requirement of complete bilateral pelvic and para-aortic lymphadenectomy is not settled.)[59] for FIGO stage IA and IC disease.

3.4 Malignant ovarian germ cell tumor (MOGCT)

Malignant germ cell tumors occur in around 1% - 4% of the ovarian cancer patients and are usually diagnosed in adolescents and young women, who are mostly in FIGO stage IA disease. MOGCT are associated with a highly favorable prognosis. It is evidently regarded with a 5-year survival rate as high as 94% for early-stage disease, and an 84% 5-year survival rate overall(67). For patients with MOGCT, thoughts to the chemo responsive nature of the tumors, the standard of care and should be performed, regardless of the stage(68), USO and comprehensive surgical staging (examination and palpation of the omentum and resection, examination and palpation of the iliac and aorto-caval nodes are recommended[59]. From a systematic review, the fecundity rate was 24.6% and 80% of the patients trying to conceive succeeded at least one pregnancy[69].

Summary

All newly diagnosed, early-stage gynecologic cancer patients who are in their reproductive years and classified as the candidates for fertility sparing treatments should be promptly referred to the reproductive specialists as soon as possible; since the initiation treatment planning. Early referral facilitates the patient's realization of her chance of fertility, as well as the factors that might affect it. In addition, the counselling provides the extensive details of the fertility preservation options and the available ART. Pre-treatment counselling substantially impacts the decision-making which is mainly based on the fertility risks from the treatments and an alternative in case of the failed conservative management. Patients should be insistently informed that the fertility sparing treatment is not the standard of care and accepted possibilities of impaired survival. The doctors should emphasize on a comprehensive surveillance and a complete surgical staging following family completion must be achieved.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Moser EC, Meunier F. Cancer survivorship: A positive side-effect of more successful cancer treatment. EJC Suppl 2014;12:1-4.
3. Duffy C, Allen S. Medical and psychosocial aspects of fertility after cancer. Cancer J 2009;15:27-33.
4. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36:1994-2001.
5. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019;112:1022-33.
6. Quinn GP, Vadaparampil ST, Lee JH, Jacobsen PB, Bepler G, Lancaster J, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. J Clin Oncol 2009;27:5952-7.
7. Chan JL, Letourneau J, Salem W, Cil AP, Chan SW, Chen LM, et al. Regret around fertility choices is decreased with pre-treatment counseling in gynecologic cancer patients. J Cancer Surviv 2017;11:58-63.
8. Thomson AB, Critchley HO, Kelnar CJ, Wallace WH. Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Pract Res Clin Endocrinol Metab 2002;16:311-34.
9. Critchley HO, Bath LE, Wallace WH. Radiation damage to the uterus -- review of the effects of treatment of childhood cancer. Hum Fertil (Camb) 2002;5:61-6.
10. Infertility workup for the women's health specialist: ACOG Committee Opinion, Number 781. Obstet Gynecol 2019;133:e377-e84.
11. Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril

2016;105:755-64.e8.
12. Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. Fertil Steril 2016;105:459-66.e2.
13. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril 2018;110:380-6.
14. Oktay K, Harvey BE, Loren AW. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update Summary. J Oncol Pract 2018;14:381-5.
15. Pacheco F, Oktay K. Current success and efficiency of autologous ovarian transplantation: a meta-analysis. Reprod Sci 2017;24:1111-20.
16. Buonomo B, Multinu F, Casarin J, Betella I, Zanagnolo V, Aletti G, et al. Ovarian transposition in patients with cervical cancer prior to pelvic radiotherapy: a systematic review. Int J Gynecol Cancer 2021;31:360-70.
17. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015;372:923-32.
18. Demeestere I, Brice P, Peccatori FA, Kentos A, Dupuis J, Zachee P, et al. No Evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. J Clin Oncol 2016;34:2568-74.
19. Cancer STAT facts: cervical cancer. National Cancer Institute, Surveillance, Epidemiology, and End Results Program.2020 [Internet]. Jun 30, 2020 [cited 2020 Jun 30]. Available from: https://seer.cancer.gov/statfacts/html/cervix.html.
20. Abu-Rustum NR, Yashar CM, Bean S, Bradley K, Campos SM, Chon HS, et al. NCCN Guidelines Insights: Cervical cancer, Version 1.2020. J Natl Compr Canc Netw 2020;18:660-6.
21. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006;367:489-98.
22. Gwacham NI, McKenzie ND, Fitzgerald ER, Ahmad S, Holloway RW. Neoadjuvant chemotherapy followed by fertility sparing surgery in cervical cancers size 2-4 cm; emerging data and future perspectives. Gynecol Oncol 2021;162:809-15.
23. Shah JS, Jooya ND, Woodard TL, Ramirez PT, Fleming ND, Frumovitz M. Reproductive counseling and pregnancy outcomes after radical trachelectomy for early stage cervical cancer. J Gynecol Oncol 2019;30:e45.
24. Stewart K, Campbell S, Frumovitz M, Ramirez PT, McKenzie LJ. Fertility considerations prior to conservative management of gynecologic cancers. Int J Gynecol Cancer 2021;31:339-44.
25. Nezhat C, Roman RA, Rambhatla A, Nezhat F. Reproductive and oncologic outcomes after fertility-sparing surgery for early stage cervical cancer: a systematic review. Fertil Steril 2020;113:685-703.
26. Practice Bulletin No. 149: Endometrial cancer. Obstet Gynecol 2015;125:1006-26.
27. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril 2017;107:840-7.
28. Nitecki R, Woodard T, Rauh-Hain JA. Fertility-sparing treatment for early-stage cervical, ovarian, and endometrial malignancies. Obstet Gynecol 2020;136:1157-69.
29. Obermair A, Baxter E, Brennan DJ, McAlpine JN, Muellerer JJ, Amant F, et al. Fertility-sparing treatment in early endometrial cancer: current state and future strategies. Obstet Gynecol Sci 2020;63:417-31.
30. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol 2005;105:575-80.
31. Shih KK, Garg K, Levine DA, Kauff ND, Abu-Rustum NR, Soslow RA, et al. Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. Gynecol Oncol 2011;123:88-94.
32. Cosgrove CM, Cohn DE, Hampel H, Frankel WL, Jones D, McElroy JP, et al. Epigenetic silencing of MLH1 in endometrial cancers is associated with larger tumor volume, increased rate of lymph node positivity and reduced recurrence-free survival. Gynecol Oncol 2017;146:588-95.
33. Cohn DE, Frankel WL, Resnick KE, Zanagnolo VL, Copeland LJ, Hampel H, et al. Improved survival with an intact DNA mismatch repair system in endometrial cancer. Obstet Gynecol 2006;108:1208-15.
34. Leitao MM, Jr., Kehoe S, Barakat RR, Alektiar K, Gattoc LP, Rabbitt C, et al. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol 2009;113:105-8.
35. Di Spiezio Sardo A, De Angelis MC, Della Corte L, Carugno J, Zizolfi B, Guadagno E, et al. Should endometrial biopsy under direct hysteroscopic visualization using the grasp technique become the new

gold standard for the preoperative evaluation of the patient with endometrial cancer? Gynecol Oncol 2020;158:347-53.
36. Lago V, Martín B, Ballesteros E, Cárdenas-Rebollo JM, Minig L. Tumor grade correlation between preoperative biopsy and final surgical specimen in endometrial cancer: the use of different diagnostic methods and analysis of associated factors. Int J Gynecol Cancer 2018;28:1258-63.
37. Larish A, Kumar A, Weaver A, Mariani A. Impact of hysteroscopy on course of disease in high-risk endometrial carcinoma. Int J Gynecol Cancer 2020;30:1513-9.
38. Zarbo G, Caruso G, Caruso S, Mangano U, Zarbo R. Endometrial cancer: preoperative evaluation of myometrial infiltration magnetic resonance imaging versus transvaginal ultrasonography. Eur J Gynaecol Oncol 2000;21:95-7.
39. Concin N, Creutzberg CL, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma. Virchows Arch 2021;478:153-90.
40. Tewari KS, Di Saia PJ. Ovulatory failure, fertility preservation and reproductive strategies in the setting of gynecologic and non-gynecologic malignancies. Eur J Gynaecol Oncol 2006;27:449-61.
41. Eskander RN, Randall LM, Berman ML, Tewari KS, Disaia PJ, Bristow RE. Fertility preserving options in patients with gynecologic malignancies. Am J Obstet Gynecol 2011;205:103-10.
42. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012;125:477-82.
43. Wei J, Zhang W, Feng L, Gao W. Comparison of fertility-sparing treatments in patients with early endometrial cancer and atypical complex hyperplasia: A meta-analysis and systematic review. Medicine (Baltimore) 2017;96:e8034.
44. Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer 2005;15:974-8.
45. Erkanli S, Ayhan A. Fertility-sparing therapy in young women with endometrial cancer: 2010 update. Int J Gynecol Cancer 2010;20:1170-87.
46. Carugno J, Wong A. Fertility-sparing approach for endometrial cancer: the role of office hysteroscopy. Minim Invasive Ther Allied Technol 2021:30:296-303.
47. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012;122:253-70.
48. Zhang Q, Celestino J, Schmandt R, McCampbell AS, Urbauer DL, Meyer LA, et al. Chemopreventive effects of metformin on obesity-associated endometrial proliferation. Am J Obstet Gynecol 2013;209:24.e1-24.e12.
49. Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett 2001;167:39-48.
50. Matsuo K, Machida H, Shoupe D, Melamed A, Muderspach LI, Roman LD, et al. Ovarian conservation and overall survival in young women with early-stage low-grade endometrial cancer. Obstet Gynecol 2016;128:761-70.
51. Jia P, Zhang Y. Ovarian preservation improves overall survival in young patients with early-stage endometrial cancer. Oncotarget 2017;8:59940-9.
52. Cancer STAT facts: ovarian cancer. National Cancer Institute, Surveillance, Epidemiology, and End Results Program 2020. [Internet]. Jun 30, 2020 [cited 2020 Jun 30]. Available from: https://seer.cancer.gov/statfacts/html/ovary.html.
53. Shah JS, Mackelvie M, Gershenson DM, Ramalingam P, Kott MM, Brown J, et al. Accuracy of intraoperative frozen section diagnosis of borderline ovarian tumors by hospital type. J Minim Invasive Gynecol 2019;26:87-93.
54. Park JY, Lee SH, Kim KR, Kim YT, Nam JH. Accuracy of frozen section diagnosis and factors associated with final pathological diagnosis upgrade of mucinous ovarian tumors. J Gynecol Oncol 2019;30:e95.
55. Tomao F, Peccatori F, Del Pup L, Franchi D, Zanagnolo V, Panici PB, et al. Special issues in fertility preservation for gynecologic malignancies. Crit Rev Oncol Hematol 2016;97:206-19.
56. Melamed A, Rizzo AE, Nitecki R, Gockley AA, Bregar AJ, Schorge JO, et al. All-cause mortality after fertility-sparing surgery for stage I epithelial ovarian cancer. Obstet Gynecol 2017;130:71-9.
57. Sinno AK, Fader AN, Roche KL, Giuntoli RL, 2nd, Tanner EJ. A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer. Gynecol Oncol 2014;134:281-6.
58. Fruscio R, Ceppi L, Corso S, Galli F, Dell'Anna T, Dell'Orto F, et al. Long-term results of fertility-sparing treatment compared with standard radical surgery for early-stage epithelial ovarian cancer. Br J Cancer 2016;115:641-8.
59. Santos ML, Pais AS, Almeida Santos T. Fertility

preservation in ovarian cancer patients. Gynecol Endocrinol 2021;37:483-9.
60. Skírnisdóttir I, Garmo H, Wilander E, Holmberg L. Borderline ovarian tumors in Sweden 1960-2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer 2008;123:1897-901.
61. Lou T, Yuan F, Feng Y, Wang S, Bai H, Zhang Z. The safety of fertility and ipsilateral ovary procedures for borderline ovarian tumors. Oncotarget 2017;8:115718-29.
62. Trillsch F, Mahner S, Woelber L, Vettorazzi E, Reuss A, Ewald-Riegler N, et al. Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. Ann Oncol 2014;25:1320-7.
63. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Berchuck A, et al. Ovarian cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:191-226.
64. Rao GG, Skinner EN, Gehrig PA, Duska LR, Miller DS, Schorge JO. Fertility-sparing surgery for ovarian low malignant potential tumors. Gynecol Oncol 2005;98:263-6.
65. Plett H, Harter P, Ataseven B, Heitz F, Prader S, Schneider S, et al. Fertility-sparing surgery and reproductive-outcomes in patients with borderline ovarian tumors. Gynecol Oncol 2020;157:411-7.
66. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol 2003;21:1180-9.
67. Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, et al. Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 2006;107:1075-85.
68. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. Gynecol Oncol 1994;55:S62-72.
69. Morrison A, Nasioudis D. Reproductive outcomes following fertility-sparing surgery for malignant ovarian germ cell tumors: a systematic review of the literature. Gynecol Oncol 2020;158:476-83.

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OBSTETRICS

Cold Pack Compression to the Lower Abdomen after Childbirth to Reduce Blood Loss in Women Undergoing Vaginal Delivery: A randomized controlled trial

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ABSTRACT

Objectives: To determine the efficacy of cold pack compression to the lower abdomen after childbirth until 2 hours postpartum to reduce blood loss.

Materials and Methods: Sixty singleton pregnant women who underwent normal delivery at Khon Kaen Hospital between February and June 2020 were randomly allocated to two groups, one receiving cold pack compression to the lower abdomen after childbirth until 2 hours postpartum (n = 30) versus standard vaginal delivery (n = 30). The respective amount of blood loss in both groups was measured from after childbirth until 2 hours postpartum by calculating the total weight of blood from the blood collecting bag and diapers. Additional blood transfusion, adverse events from the cold pack, and the after-pain score were recorded.

Results: Baseline characteristics between groups were comparable. Mean blood loss in the cold pack compression group was significantly lower than the standard vaginal delivery group (183.87 ± 76.52 vs. 271.36 ± 103.80 ml, mean difference was -87.50, 95% confidence interval -134.62 to -40.37, $p < 0.001$). None of the participants in either group experienced postpartum hemorrhage or required blood transfusion. None of the participants in the cold pack compression group experienced any adverse events. There was no statistical difference in the after-pain score between groups.

Conclusion: Cold pack compression to the lower abdomen after childbirth until 2 hours postpartum could significantly reduce blood loss compared with standard vaginal delivery without serious adverse events.

Keywords: cold pack compression, vaginal delivery, blood loss.

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การวางประคบเย็นบริเวณหน้าท้องส่วนล่างหลังคลอดทารกเพื่อลดการสูญเสียเลือดในมารดาที่คลอดบุตรทางช่องคลอด: การศึกษาแบบสุ่มมีกลุ่มเปรียบเทียบ

ฐปนพ ธนสมทบชนมน, สาธิดา จันทนวิลัย, ภัทรพร ตั้งกีรติชัย

บทคัดย่อ

วัตถุประสงค์: *ศึกษาผลของการวางประคบเย็นบริเวณหน้าท้องส่วนล่างหลังคลอดทารกจนถึง 2 ชั่วโมงหลังคลอด เพื่อลดการสูญเสียเลือด*

วัสดุและวิธีการ: *สตรีตั้งครรภ์เดี่ยวครบกำหนดคลอดทางช่องคลอดที่โรงพยาบาลขอนแก่น ระหว่างเดือนกุมภาพันธ์ ถึงมิถุนายน 2563 กลุ่มตัวอย่างทั้งหมด จำนวน 60 ราย ถูกแบ่งเป็นกลุ่มทดลอง และกลุ่มควบคุม โดยวิธีการสุ่มกลุ่มละ 30 ราย กลุ่มทดลองได้รับการประคบเย็นที่บริเวณหน้าท้องส่วนล่างหลังคลอดทารกจนถึง 2 ชั่วโมงหลังคลอด การวัดปริมาณเลือดทำได้โดยการคำนวณน้ำหนักจากถุงตวงเลือด และผ้าอนามัยที่ใช้ใส่ซับเลือดก่อนและหลังการใช้ รวมถึงสังเกตการได้รับเลือดภายหลังคลอด ผลข้างเคียงของการประคบเย็นและอาการปวดท้องหลังคลอด*

ผลการศึกษา: *ลักษณะพื้นฐานของกลุ่มตัวอย่างมีลักษณะไม่แตกต่างกัน ปริมาณการสูญเสียเลือดในกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (กลุ่มทดลองค่าเฉลี่ยเท่ากับ 183.87 มิลลิลิตร, กลุ่มควบคุมค่าเฉลี่ยเท่ากับ 271.36 มิลลิลิตร, ผลต่างค่าเฉลี่ยเท่ากับ 87.50 มิลลิลิตร, ระดับความเชื่อมั่นร้อยละ 95 คือ - 134.62 ถึง - 40.37, $p < 0.001$) ไม่พบอุบัติการณ์ของการตกเลือดหลังคลอด การได้รับเลือดหลังคลอดหรืออาการข้างเคียงจากการประคบเย็นในกลุ่มตัวอย่างและไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระดับความปวดบริเวณช่องท้องหลังคลอด*

สรุป: *การวางประคบเย็นบริเวณหน้าท้องส่วนล่างหลังคลอดทารกจนถึง 2 ชั่วโมงหลังคลอด สามารถลดปริมาณการสูญเสียเลือดได้อย่างมีประสิทธิผลเปรียบเทียบกับการคลอดทารกทางช่องคลอดปกติ และไม่พบภาวะแทรกซ้อนที่อันตราย*

คำสำคัญ: *การวางประคบเย็น, การคลอดทารกทางช่องคลอด, การสูญเสียเลือด*

Introduction

Maternal mortality remains unacceptably high. About 295,000 women died worldwide during and following pregnancy and childbirth in 2017, and the vast majority were preventable[1]. Nearly 75% of all maternal deaths are due to severe bleeding, infections, high blood pressure during pregnancy, complications from delivery, and unsafe abortion[2]. In the current study, we focused on severe bleeding after childbirth, which can kill a healthy woman within hours if she is unattended.

Postpartum hemorrhage (PPH) is a primary cause of maternal mortality. PPH accounts for about 20% of all cases of maternal death[3]. PPH is defined as blood loss of 500 ml or more within 24 hours after vaginal birth, mostly due to uterine atony[4]. Active management of the third stage of labor can reduce the incidence of PPH. Administration of uterotonic agents, placental delivery by control cord traction, and uterine massage are recommended for the prevention of PPH[5]. Even if all these methods are used, postpartum hemorrhage continue to be reported.

Mitchell et al[6] studied the effect of ice pack compression directly to the uterus during cesarean section to reduce intra-operative blood loss and found that the amount of blood loss in the intervention group was significantly lower than the control group. Another study on directly cooling the uterus during cesarean section from Nawasirodom et al[7], reveled a statistically significant reduction in intra-operative blood loss in the uterine cooling group compared with the routine cesarean section group. In contrast, in the only recent study about the effect of cold compression to reduce blood loss during vaginal delivery, Masuzawa et al[8], showed that cooling the lower abdomen with an icepack after placental delivery did not decrease blood loss among women who had a vaginal delivery with no prophylactic uterotonic in the third stage of labor. They also found that cooling the lower abdomen seemed to increase the amount of blood loss; however, data collection was after placental delivery which may not properly represent intrapartum blood loss. According to the normal physiology of vaginal delivery, blood loss mostly occurs from the detachment of placental spiral arteries during placental delivery. In our study, we aimed to collect blood loss data before placental delivery. Excessive maternal weight should, moreover, be excluded from the study because the thickness of the maternal subcutaneous fat layer can interfere with the result. In Japan, cold compression of the lower abdomen was used for post-vaginal delivery to decrease blood loss and prevent PPH[9]; however, the efficacy of the method was not well-established. The efficacy of cold compression to reduce blood loss in vaginal delivery thus remains unclear due to insufficient data. The current study's primary objective was to evaluate the efficacy of cold pack compression to the lower abdomen after childbirth until 2 hours postpartum to reduce blood loss in women who undergo vaginal delivery compared with standard vaginal delivery. The secondary objectives were to evaluate the additional blood transfusion, adverse events from cold pack compression, and after-pain score.

Materials and Methods

This randomized controlled trial was performed at the Department of Obstetrics and Gynecology, Khon Kaen Hospital, Thailand, between February and June 2020. Ethical approval was granted by the Khon Kaen Hospital Institute Review Board for Human Research. The eligible women were informed about the study, and written consent was obtained after admission to the labor room. The inclusion criteria were term pregnancy women, singleton pregnancy, cephalic presentation, spontaneous vaginal delivery, and maternal body mass index (BMI) at delivery < 30 kg/m^2. The exclusion criteria were maternal medical conditions, placental abnormalities, delivery by operative vaginal delivery, obstetric complications, or obstetric trauma.

The participants were randomized by a computer-generated block of four prepared in numbered sealed envelopes. The allocation was

performed by opening the envelope after childbirth and assigning the participant to the cold pack compression group or the standard vaginal delivery group. The study was blinded only to the researchers until the data were analyzed. For the study group, a 24 x 11 cm cold pack (3M Nexcare® reusable cold/hot pack) was compressed to the lower abdomen at the uterus after delivery of the fetus. The pubic symphysis was used as the landmark. Each cold pack was cooled in a freezer for more than 4 hours to provide a contact temperature of 6.4°C (± 0.2°C). The cold pack was covered with a single layer of toweling before it was placed on the lower abdomen, and it was changed every 30 minutes until 2 hours postpartum. If women in the study group felt discomfort from the cold pack or any adverse events from the cold pack (i.e., frostbite, blister of skin, or numbness), it was removed. All women received active management of the third stage of labor (oxytocin 10 units intramuscular injection after delivery of the fetus's anterior shoulder, cutting and clamping cord shortly after fetal birth, and placental delivery by control cord traction).

So as to minimize any contamination, before blood collection the amniotic fluid and meconium were wiped away from the perineum and vagina using an antiseptic agent. The blood collection bag was placed under the buttocks to collect blood from placental delivery until any episiotomy wound was repaired or perineal wound was checked. The participants were then transferred to the labor room's observational zone; then, blood loss was collected by diaper until 2 hours postpartum. After 2 hours postpartum, the after-pain score was assessed by each patient using the visual analogue scale before they were transferred to the postpartum ward. Blood loss was measured by the weight of the blood collecting bag, gauze, and diapers after being used subtracted by the weight of unused materials. The calculated value was weight in grams to milliliters (1.05 g to 1 ml)[10].

The quantity of blood (ml) = (weight of used materials - weight of unused materials)/1.05.

Baseline characteristics of all participants were recorded, including maternal age, gestational age, parity, BMI, duration of the second stage of labor, duration of the third stage of labor, oxytocin for augmentation, degree of perineal tear, and neonatal birth weight.

The primary outcome was the amount of blood loss from the third stage of labor until 2 hours postpartum. Additional blood transfusion, adverse events from a cold pack, and after-pain score were recorded.

The sample size was calculated based on a pilot study done in the labor room of Khon Kaen Hospital with 15 participants per group. Mean blood loss in the cold pack compression group was 198.5 ml compared with 294.1 ml in the control group (standard deviation 118.14 ml). We used a formula to test the difference between two independent means with a one-sided alpha error of 0.05, a power of 80%, and a 10% drop-out rate. The resulting sample size was 30 participants per group. Data were analyzed using STATA Version 13.0 statistical software. Differences in continuous variables were analyzed using the student t-test and were presented as means with standard deviation. Categorical variables were analyzed using the chi-square and Fisher's exact tests and presented as percentages.

Results

Sixty-seven eligible women who vaginally delivered at Khon Kaen Hospital's labor room between February and June 2020 were initially enrolled in the study. Seven participants were excluded due to third- and fourth-degree perineal tears and delivered by operative vaginal delivery. Sixty women were equally randomized into two groups: the cold pack compression group and the standard vaginal delivery group. The study flow diagram is shown in Fig 1. The demographic and clinical characteristics between groups were not different vis-à-vis maternal age, gestational age, parity, BMI, duration of the second stage of labor, duration of the third stage of labor, oxytocin for augmentation, degree of perineal tearing, or neonatal birth weight (Table 1).

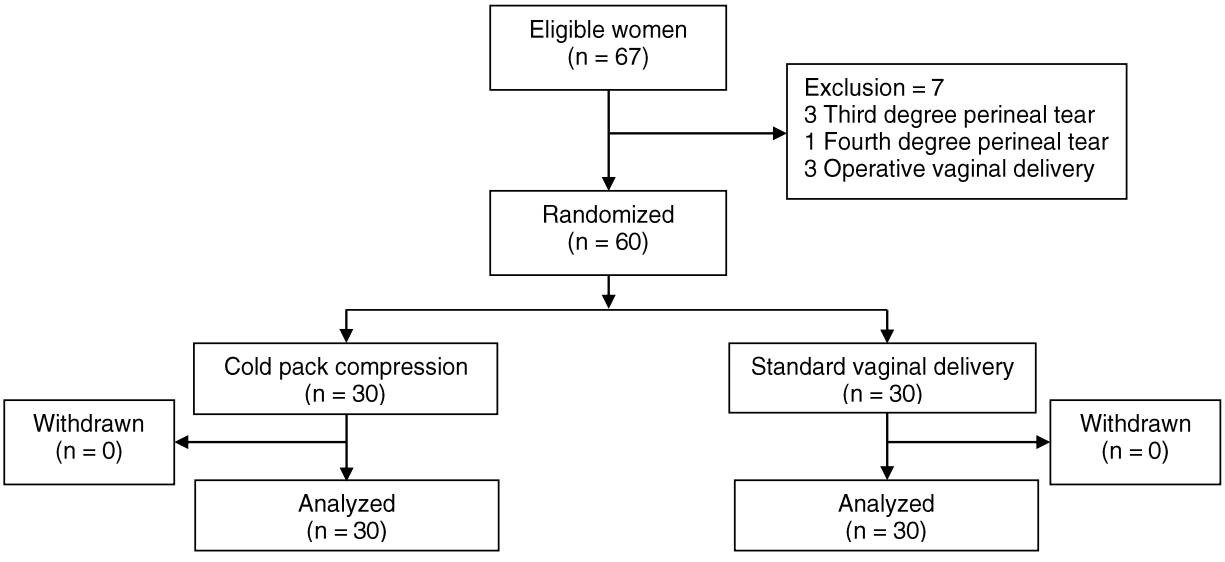

Fig. 1. Study flow diagram.

Table 1. Baseline characteristics of the study participants.

Characteristics	Cold pack compression (n = 30)	Standard vaginal delivery (n = 30)	p value
Maternal age (years), mean ± SD	26.8 ± 6.2	26.1 ± 5.5	0.64
Gestational age (weeks), mean ± SD	38.1 ± 0.9	39.1 ± 1.1	0.07
Parity (%)			0.43
Nulliparous	18 (60.0)	18 (60.0)	
Multiparous	12 (40.0)	12 (40.0)	
Maternal BMI (kg/m²) mean ± SD	26.0 ± 2.5	25.2 ± 2.8	0.24
Duration of the second stage of labor (mins), mean ± SD	13.9 ± 1.9	14.1 ± 1.3	0.92
Duration of the third stage of labor (mins), mean ± SD	2.63 ± 0.85	2.57 ± 0.73	0.74
Oxytocin for augmentation (%)			0.79
No	19 (63.3)	18 (60.0)	
Yes	11 (36.7)	12 (40.0)	
Perineal tear (%)			0.42
None	2 (6.7)	4 (13.3)	
First degree	0	1 (3.3)	
Second degree	28 (93.3)	25 (83.4)	
Birth weight (grams), mean ± SD	2989.3 ± 302.1	3067.6 ± 298.7	0.24

SD: standard deviation

Mean blood loss after childbirth until 2 hours postpartum was significantly lower in the cold pack compression group compared with the standard vaginal delivery group (183.87 ± 76.52 and 271.36 ± 103.80 ml, mean difference was -87.50 ml 95% confidence interval (CI) -134.62 to -40.37; p < 0.001). There were no participants in either group who had postpartum hemorrhage or requiring blood transfusion. No participants in the cold pack compression group had any adverse events from cold pack compression. The respective after-pain score between groups was not statistically different. The study outcomes was shown in Table 2.

Table 2. Study outcomes compared between cold pack compression group and standard vaginal delivery group.

Outcomes	Cold pack compression (n = 30)	Standard vaginal delivery (n = 30)	Mean difference	p value	95%CI
Blood loss (ml), mean ± SD	183.8 ± 76.5	271.3 ± 103.8	87.5	< 0.001	-134.6 to - 40.37
After pain score, mean ± SD	3.1 ± 1.0	3.1 ± 1.1	-	0.81	-

SD: standard deviation, CI: confidence interval

Discussion

Mean blood loss after childbirth until 2 hours postpartum was significantly lower in the cold pack compression group compared to the standard vaginal delivery group (183.87 ± 76.52 and 271.36 ± 103.80 ml, mean difference was -87.50 ml 95%CI -134.62 to -40.37; p < 0.001). The result agreed with Mitchell et al who studied the efficacy of ice pack compression directly to the uterus during cesarean section to reduce intra-operative blood loss. Mitchell et al found that the amount of blood loss in the intervention group (ice pack group) was 29% less than the control group and the incidence of PPH was 57% less in the intervention group. In a study by Nawasirodom et al on directly cooling the uterus during cesarean section revealed that there was a significant reduction in intra-operative blood loss in the uterine cooling group when compared with the routine cesarean section group (252.8 ± 133.8 vs. 472.9 ± 201.8 ml, mean difference 220 ml 95%CI 166.6 to 273.5; p < 0.001). According to the literature review, the effect of cold from cold pack compression improves myometrium contraction. Based on the science of muscle contraction, the latter occurs during the release of calcium ions from the sarcoplasmic reticulum (SR), while muscle relaxation occurs during the re-uptake of calcium ions. Cold can improve muscle contraction by slowing the re-uptake of calcium ions in smooth muscle cells[11-13]. The cold also causes blood vessels within the smooth muscles to constrict, which subsequently decreases blood flow through sympathetic innervation. This system's neurotransmitters are norepinephrine and epinephrine, which are secreted into the blood vessels, resulting in vasoconstriction[14].

In contrast, from the only recent study about the effect of cold compression to reduce blood loss in women undergoing vaginal delivery in Japan, Masuzawa et al[8], showed that cooling the lower abdomen with an icepack after placental delivery did not decrease blood loss among women who had a vaginal delivery with no prophylactic uterotonic. Notwithstanding, Masuzawa et al[8], reported that cooling the lower abdomen seemed to increase blood loss (513.3 ± 333.2 vs. 478.1 ± 310.1 ml, mean difference 35.2 ml 95%CI -65.3 to 135.7; p = 0.49), albeit the results were not statistically significant and therefore mooted. A primary difference between the

study by Masuzawa et al[8], and our study was the timing of the collected blood loss. In our study, cold pack compression was performed then blood loss was collected before delivery of the placenta. In the normal physiology of vaginal delivery, blood loss mostly occurs from the placenta's spiral arteries, which detach from the myometrium. Consequently, cooling of the lower abdomen is performed to evaluate blood loss and blood collection, and these measures should be started before placental delivery to evaluate the amount of blood loss correctly.

There was no significant difference vis-à-vis requiring blood transfusion, adverse events from cold pack compression, or the after-pain score between groups.

The study's strength was the measurement of blood loss calculated by converting the weight of blood into a volume that provided a measured amount of blood loss instead of an estimate. Limitations of the study were (a) that it was not blinded to the health care providers or participants and (b) it only collected data 2 hours postpartum for analysis, which may not represent all the incidents of PPH that can occur up to 24 hours postpartum.

Conclusions

Cold pack compression to the lower abdomen after childbirth until 2 hours postpartum could significantly reduce blood loss compared with standard vaginal delivery without serious adverse events.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Trends in maternal mortality: 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group, and the United Nations Population Division. Geneva: World Health Organization 2019.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels JD, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2:e323-33.
3. Cunningham FG, Leveno KJ, Bloom S, Spong CY, Dashe JS, Hoffman BL, et al. Williams obstetrics. 25th ed. New York: McGraw-Hill Medical 2018:755-802.
4. Weeks A. The prevention and treatment of postpartum haemorrhage: what do we know, and where do we go to next? BJOG 2015;122:202-10.
5. World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. 2012:4-7.
6. Mitchell JL, Stecher J, Crowson J, Rich D. Uterine cooling during cesarean delivery to reduce blood loss and incidence of postpartum hemorrhage: a randomized controlled trial. Obstet Gynecol 2015;125:9s-10s.
7. Nawasirodom N, Sangkomkamhang U, Sangkomkamhang T. Uterine cooling during cesarean section to reduce intraoperative blood loss: a randomized controlled trial. Thai J Obstet Gynaecol 2019;27:47-53.
8. Masuzawa Y, Kataoka Y, Nakamura S, Yaju Y. Cooling the lower abdomen to reduce postpartum blood loss: A randomized controlled trial. PLoS One 2017;12:e0186365.
9. Kataoka Y, Nakayama K, Yaju Y, Eto H. Comparison of policies for the management of care for women and newborns during the third stage of labour among Japanese hospitals, clinics and midwifery birth centers. Int J Childbirth 2015;5:200-9.
10. Waite NG. Blood components. In: Rhoades RA, Bell DR, editors. Medical physiology: principles for clinical medicine. 4th ed. Philadelphia: Lippincott Williams &Wilkins 2013:166-87.
11. Wray S, Jones K, Kupittayanant S, LI Y, Matthew A, Monir-Bishty E, et al. Calcium signaling and uterine contractility. J Soc Gynecol Investig 2003;10:252-64.
12. Wray S, Kupittayanant S, Shmigol T. Role of the sacroplasmic reticulum in uterine smooth muscle. Novartis Found Symp 2002;246:6-18.
13. Sunano S. The effects of Ca antagonists, manganese and lanthanum on cooling-induced contracture of depolarized vas deferens. Jpn J Pharmacol 1984;34: 51-6.
14. Galloway KM. Cryotherapy and moist heat. In: Jeffrey DP, David AB, eds. Orthopaedic physical therapy secrets. 3rd ed. St. Louis, Missouri: Elsevier Inc;2017:54-9.

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OBSTETRICS

Comparison of Clinical Characteristics and Prognostic Markers in Pregnant Women during the First and Second Wave of COVID-19 in India

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ABSTRACT

Objectives: The world is experiencing unprecedented challenges from the coronavirus pandemic. There is a sparse data on Coronavirus disease-2019 (COVID-19) outcomes in pregnant women from India, especially during the second wave. We aimed to compare maternal clinical characteristics and prognostic markers during first and second waves of COVID-19 and to know the correlation of the laboratory markers with disease severity and to assess maternal and perinatal outcomes.

Materials and Methods: This prospective study of COVID-19 positive pregnant women was conducted at a tertiary care hospital in India from the 1st of August 2020 to the 30th of June 2021. Data on epidemiological history, clinical presentation, laboratory results, and maternal-fetal outcome in the first and second waves of the COVID-19 pandemic were collected and analyzed.

Results: One hundred eighteen patients participated in our study, with 64 belonging to the 1st wave and 54 in the 2nd wave. Fever and sore throat were common presenting symptoms, most women with bronchial asthma and cardiac disease progressed to severe/ critical illness. C-reactive protein, lactate dehydrogenase ($p < 0.05$ in both waves), ferritin ($p < 0.01$ in 2nd wave), and procalcitonin ($p < 0.05$ in 1st wave) positively correlated with the severity of the disease.

Conclusion: Our study showed that the clinical characteristics and severity of the disease did not differ significantly in both the waves. The adverse fetal outcome was significantly more in mothers with severe and critical disease. Laboratory markers correlated significantly with the severity of the maternal disease, hence can be used as prognostic indicators.

Keywords: COVID-19, pandemic, pregnancy, laboratory parameters, India.

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Introduction

COVID-19, a global public health emergency, is caused by enveloped, positive-sense single-stranded RNA viruses called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Though the number of COVID-19 positive cases in India was low, to begin with, the situation surprisingly changed in the second wave, when over 400,000 confirmed cases/day were reported. Lineage analysis in India showed the emergence of new SARS-CoV-2 variants, i.e., B.1.617.1 (kappa) and B.1.617.2 (delta), during April–May 2021[2]. Frequent hospital visits and alterations in cell-mediated immunity predispose pregnant women to respiratory and other infections[3].

Though initial studies of COVID-19 did not demonstrate significant adverse effects on pregnant women, subsequent studies indicated greater severity of the infection and need for intensive care unit (ICU) admissions in them[4-6].

Evidence on the correlation between the severity of COVID-19 and laboratory markers in the general population is established[7, 8]. However, there is limited evidence on the correlation of these prognostic markers in the pregnant COVID-19 cohort. The prognostic indicators used in other populations cannot be extrapolated to pregnant mothers as pregnancy in itself modifies many of these parameters[3].

With the above background, we aimed to study COVID-19 pregnancies in the Indian population. Our primary objective was to compare maternal clinical characteristics and prognostic markers during first and second waves of COVID-19. Secondary objectives were to know the correlation of the laboratory markers with disease severity and to assess maternal and perinatal outcomes of COVID-19 deliveries.

Materials and Methods

Study design and setting

A prospective study was conducted at Shri Dharmasthala Manjunatheshwara College of medical sciences and hospital Dharwad, Karnataka. A total of one hundred and eighteen COVID-19 positive pregnant women participated in the study. Patients enrolled from August 1, 2020, to January 31, 2021 (sixty-four patients) and February 1 to June 30, 2021 (fifty-four patients) constituted the two successive waves, respectively.

COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or rapid antigen test (RAT). After obtaining prior written informed consent, women with singleton/multiple gestations, all trimesters, and with/without comorbidities were included, while those who denied consent were excluded from the study. Nasal or pharyngeal swabs were used for the RT-PCR test. The Institutional ethics committee (IEC) approval was taken for the study with institutional review board number- SDMIEC: 79:2020.

Data collection

Data was collected on epidemiological history, clinical presentation, and laboratory test results. Epidemiological details included age, parity, and gestational age; clinical presentation included information on presenting symptoms, maternal comorbidities, vital parameters, and clinical severity (according to classification by National Institute of Health)[9]; laboratory parameters assessed were hemoglobin (Hb), total leukocyte count (TLC), lymphocytes and platelet count, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin, urea, and creatinine. Chest x-ray was evaluated for features of pneumonia. Additionally, maternal details like need of oxygen support, mode of delivery, complications, and newborn details like weight, 5 minutes Apgar score, outcomes [intrauterine death (IUD), stillbirths, miscarriages, neonatal death, and RT-PCR results] were noted.

Statistical analysis

The first and second wave data were entered in separate excel sheets with an exclusive code assigned to all non-available/not reported data. Statistical analysis was done using IBM SPSS version 25. Descriptive data for continuous and categorical data were represented as mean ± standard deviation and proportions (%), respectively. The comparison of maternal and fetal outcomes and maternal severity between the two waves was made using chi-square test. Spearman's correlation was used for evaluating the relation between mothers'

clinical severity and their laboratory parameters. A p value of < 0.05 was considered significant for all analyses.

Results

One hundred eighteen patients participated in our study, with 64 belonging to the 1st wave and 54 in the 2nd wave.

Descriptive data

The mean age of the mothers was 28 years, with a more significant proportion of them at term gestation. The proportion of primigravida was significant in the second wave compared to the first wave. Fever and upper respiratory tract infections were the common presenting symptoms. Risks in pregnancy were comparable in both groups. Around 25% showed features of pneumonia in a chest x-ray. Pregnant women with mild to moderate disease were treated with antibiotics and supportive care. Patients with severe and critical diseases were managed with steroids, remdesivir, low molecular weight heparin (LMWH), and antimicrobials. Of the total 118 patients, two patients were given oxygen support via face mask, while other 9 with non-re-breather mask (NRBM). Non-invasive ventilation (NIV) by continuous positive airway pressure (CPAP), was required in 03/118 (2.5%) patients and invasive ventilation was required in 4/118 (3.4%) patients. The low transverse cesarean section (LTCS) was the most common mode of delivery (83% of the first wave and 60% of the second wave). A total of 7 neonates required NICU admission because of a low Apgar score. Seventeen babies had a birth weight of less than 2,500 grams, though RT-PCR of the neonate was positive in a very negligible number (Table 1). Two maternal deaths were seen in the study period. One was a 28-year-old primigravida with bronchial asthma with early pregnancy, and the other was a 30-year primigravida with severe preeclampsia. Both presented with critical COVID-19 disease requiring mechanical ventilation and died due to non-resolving infection.

Table 1. Patient characteristics for the 1st and 2nd COVID-19 waves.

Variables	Values		p value
	1st wave (n = 64)	2nd wave (n= 54)	
Age	27.89 ± 4.66	27.70 ± 4.78	0.83
Gestational age			0.36
Pre-term	17 (26.6)	10 (18.5)	
Term	46 (71.9)	44 (81.5)	
Early pregnancy	1 (1.6)	0 (0)	
Parity-primi	16 (25)	23 (42.6)	0.04*
Chief complaints			
Fever	19 (29.7)	27 (50)	0.02*
URTI	28 (43.8)	24 (44.4)	0.94
Dyspnea	13 (20.3)	2 (3.7)	0.007**
Anosmia	7 (10.9)	6 (11.1)	0.97
GI problems	7 (10.9)	6 (11.1)	0.97
Headache and myalgia	15 (23.4)	11 (20.4)	0.68
Risk in pregnancy			
Preeclampsia	16 (25)	7 (13)	0.1
Oligohydramnios	6 (9.4)	1 (1.9)	0.08
GDM	6 (9.4)	3 (5.6)	0.43
PTL	5 (7.8)	2 (3.7)	0.34
PROM/PPROM	13 (20.3)	15 (27.8)	0.61
Bronchial asthma	1 (1.6)	1 (1.9)	0.90
Cardiac disease	4 (6.2)	1 (1.9)	0.38

Table 1. Patient characteristics for the 1st and 2nd COVID-19 waves. (Cont.)

Variables	Values		p value
	1st wave (n = 64)	2nd wave (n= 54)	
Clinical features			
Tachycardia	9 (14.1)	10 (18.5)	0.51
Febrile	10 (15.6)	16 (29.6)	0.06
Hypertension	15 (23.4)	3 (5.6)	0.007**
Tachypnoea	13 (20.3)	12 (22.2)	0.80
Hypoxia	10 (15.6)	8 (15)	0.68
Diagnosis			0.03*
RAT	6 (9.4)	13 (24.1)	
RT PCR	58 (90.6)	41 (75.9)	
Admission			0.63
LR	48 (75)	41 (75.9)	
HDU	9 (14.1)	5 (9.3)	
ICU	7 (10.9)	8 (14.8)	
Lab parameters			
Hb gm/dl	11.26 ± 1.34	11.18 ± 1.89	0.79
TLC x109 cells/litre	13.53 ± 7.69	15.84 ± 2.46	0.47
Platelets x 109 cells/litre	229.51 ± 75.14	210.71 ± 73.85	0.17
CRP mg/dl	43.81 ± 59.68	34.87 ± 50.52	0.38
LDH IU/L	337.59 ± 215.33	430.33 ± 361.13	0.08
Ferritin ng/ml	104.83 ± 234.13	64.81 ± 57.72	0.22
Procalcitonin ng/ml	0.81 ± 6.01	64.81 ± 57.72	0.60
Urea mg/dl	23.31 ± 11.33	18.96 ± 8.88	0.02*
Creatinine mg/dl	0.66 ± 0.27	0.60 ± 0.14	0.19
Chest X-ray-pneumonia	17 (26.6)	15 (27.8)	0.88
Treatment			
Steroids	13 (20.3)	18 (33.3)	0.10
Remdesivir	3 (4.7)	8 (14.8)	0.05
LMWH	27 (42.2)	15 (27.8)	0.10
Anti-microbials	64 (100)	54 (100)	-
Oxygen support			0.14
Face mask	0 (0)	2 (3.7)	
NRBM	6 (9.4)	3 (5.6)	
NIV (CPAP)	3 (4.7)	0 (0)	0.14
Mechanical ventilation	1 (1.6)	3 (5.6)	
Mode of delivery			0.004**
PTVD	6 (9.4)	6 (11.1)	
FTVD	3 (4.7)	16 (29.6)	
LTCS	53 (82.8)	32 (59.3)	
Expulsion	1 (1.6)	0 (0)	
Baby weight in kilograms	2.74 ± 0.97	2.66 ± 0.59	0.61
5 minutes APGAR score < 7	5 (7.8)	2 (3.7)	0.25
Neonatal RTPCR positive	3 (4.7)	1 (1.9)	0.17
Prolonged hospital stay	11 (17.2)	10 (18.5)	0.64

* significant at p<0.05, ** significant at p<0.01

Primi: primigravida, URTI: upper respiratory tract infection, GI: gastrointestinal, GDM: gestational diabetes mellitus, PTL: preterm labor, PROM: premature rupture of membranes, PPROM: preterm- premature rupture of membranes, RT PCR: real-time reverse transcription-polymerase chain reaction, RAT: rapid antigen test, LR: labour room, HDU: high dependency unit, ICU: intensive care unit, Hb: hemoglobin, TLC: total leucocyte count, CRP: C reactive protein, LDH: lactate dehydorgenase, LMWH: low molecular weight heparin, NRBM: non re-breathing mask, NIV: non invasive ventilation, CPAP: continuous positive airway pressure, PTVD: pre term vaginal delivery, FTVD: full term vaginal delivery, LTCS: low transverse caesarean section.

Clinical severity vs laboratory parameters

Comparing maternal clinical severity with laboratory parameters yielded a significantly positive correlation for CRP and LDH in patients of both waves. In contrast, procalcitonin and ferritin were correlated considerably only in the first and second waves, respectively (Table 2).

Table 2. Correlation between clinical severity of mothers and their lab parameters.

Variable	Lab parameter	1st wave		2nd wave	
		Spearman's rho	p value	Spearman's rho	p value
Clinical severity	TLC	- 0.051	0.686	0.008	0.955
	Lymphocyte count	- 0.052	0.684	- 0.173	0.211
	c reactive protein	0.493**	0.000	0.512**	0.000
	LDH	0.322**	0.009	0.583**	0.000
	ferritin	- 0.085	0.503	0.438**	0.001
	Procalcitonin	0.262*	0.037	0.244	0.075

TLC: total leucocyte count, LDH: lactate dehydrogenase

Comparison of the maternal and fetal outcomes and severity of maternal disease between the two waves

Maternal complications and adverse fetal outcomes did not vary significantly during the first and the 2nd wave (Table 3). Maternal severity did not vary much across the two waves. (Table 4).

Table 3. Comparison of maternal and fetal outcome between the patients of two waves.

Outcome	n (%) in 1st wave	n (%) in 2nd wave	Chi-square	p value
Miscarriages	2 (3.1)	0 (0)	1.717	0.19
APH	1 (1.6)	4 (7.4)	6.404	0.17
Poor obstetric outcome			11.404	0.12
IUD	0 (0)	3 (5.6)		
Still birth	0 (0)	2 (3.7)		
PND	2 (3.1)	0 (0)		
Expulsion/Abortion	1 (1.6)	0 (0)		

APH: ante partum hemorrhage, IUD: intrauterine death, PND: post natal death.

Table 4. Comparison of maternal severity between the patients of two waves.

Severity	n (%) in 1st wave	n (%) in 2nd wave	Chi-square	p value
Asymptomatic	13 (20.3)	20 (37)		
Mild	34 (53.1)	19 (35.2)		
Moderate	7 (10.9)	7 (13)	5.81	0.21
Severe	8 (12.5)	5 (9.3)		
Critical	2 (3.1)	3 (5.6)		

APH: ante partum hemorrhage, IUD: intrauterine death, PND: post natal death.

In addition, it was observed that fetal complications like IUD and stillbirth were significantly greater in mothers with one or more symptoms than asymptomatic mothers. (maternal severity vs. fetal outcome; 1st wave chi-square: 49.32, $p < 0.001$; 2nd wave chi-square: 31.69, $p = 0.002$). (Table 5 and 6)

Table 5. Comparison of maternal severity between the patients of two waves.

Maternal clinical severity	Fetal outcome; n (%)								Chi square (p value)
	Live birth	LBW	IUGR	IUD	SB	PND	Miscarriage	Expulsion	
Asymptomatic	11 (84.6)	1 (7.7)	1 (7.7)	0	0	0	0	0	**49.322 (0.001)**
Mild	28 (82.4)	5 (14.7)	0	0	0	0	1 (2.9)	0	
Moderate	4 (57.1)	1 (14.3)	1 (14.3)	0	0	1 (14.3)	0	0	
Severe	7 (87.5)	0	0	0	0	1 (12.5)	0	0	
Critical	0	1 (50)	0	0	0	0	0	1	

LBW: low birth weight, IUGR: intrauterine growth restriction, IUD: intrauterine death, SB: still birth, PND: post natal death.

Table 6. Association between clinical severity of mother and fetal outcome for 2nd wave.

Maternal clinical severity	Fetal outcome; n (%)								Chi square (p value)
	Live birth	LBW	IUGR	IUD	SB	PND	Miscarriage	Expulsion	
Asymptomatic	20 (100)	0	0	0	0	0	0	0	**31.691 (0.002)**
Mild	15 (78.9)	2 (10.5)	0	1 (5.3)	1 (5.3)	0	0	0	
Moderate	3 (42.9)	2 (28.6)	0	1 (14.3)	1 (14.3)	0	0	0	
Severe	2 (40)	2 (40)	0	1 (20)	0	0	0	0	
Critical	0	3 (100)	0	0	0	0	0	0	

LBW: low birth weight, IUGR: intrauterine growth restriction, IUD: intrauterine death, SB: still birth, PND: post natal death.

Correlation between maternal severity and associated risk in pregnancy

Thirteen patients progressed to severe disease during both waves of which 4/13 (31%) were having preeclampsia, 3/13 (23%) had cardiac disease. Five of the patients had critical COVID-19 illness during both waves. Among them 2/5 (40%) of them had bronchial asthma and 1/5 (20%) had underlying cardiac illness.

Discussion

Current data on the effects of COVID-19 in pregnancy comparing the two waves are sparse. We were interested in finding differences in the clinical characteristics and maternal and fetal outcomes across the two waves and identifying laboratory markers to indicate the severity of the disease in low-resource settings.

According to an Indian study, a prevalence of 12.3% (mean 9.4, 95% confidence interval (CI) 6.6 - 12.1) was seen in pregnant women[10]. The mean maternal age of 28 years in our study was similar to other Indian studies by Sumitra Bachani et al (26 years) and Tadas et al (27 years)[11, 12].

Many studies have demonstrated that the clinical characteristics of COVID-19 in pregnant women were no different from non-pregnant adults in the general population[13].

Upper respiratory tract infection (URTI) was the most common presenting complaint during the first wave, whereas it was fever during the second wave, which agrees with other studies[11,12,14]. Patients with bronchial asthma, cardiac disease, and preeclampsia progressed to severe and critical illnesses that required ICU care and prolonged hospital stay. The same trend was even seen in studies by Nayak et al and Gajbhiye et al[16,17]. Li et al, attributed severe clinical manifestations in hypertensive patients to dysregulation of placental angiotensin-converting enzyme 2 (ACE2) at the maternal-fetal interface by SARS-CoV-2, leading to high rates of preeclampsia in them[18]. Further studies are necessary to conclude whether preeclampsia is a significant contributor to the development of severe COVID-19 infection. The fraction of women with hypertension was significant during the first wave when

compared to the second.

Almost all of them in the 1st wave (83%) and more than half of second wave patients (60%) underwent LTCS. The proportion of LTCS was slightly lesser (43%, 50%) in other studies[12, 16]. These discrepancies could have been due to urgent deliveries because of severe respiratory compromise or the fear of transmission to neonates in vaginal deliveries due to longer exposure time.

Around 3 % of neonates in our study tested positive at 48 hours which is in concordance with the findings of Facchetti and Hosier et al[19, 20]. Amniotic fluid, cord blood, neonatal throat swab, and breast milk samples have been found to be negative for SARS-CoV-2 by few studies[13]. Past studies have reported that SARS-CoV-2 has a similar receptor binding domain structure to that of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). This suggested that COVID-19 might have a similar pathogenesis to SARS-CoV-1 infection. Thus, the risk of vertical transmission might be as low as that of SARS-CoV-1[13]. Neonatal infection could be probably due to close contact with infected mothers during breastfeeding. 10% of the patients delivered preterm, which corresponds with the background risk of preterm labour in India[3].

Although diagnosis of infection by RT-PCR is considered to be gold standard and was the only method available in the initial phase of pandemic[13], later on COVID-19 RAT were made widely available. They are low cost, easy to use, and results are readily available in 15 minutes, hence are an excellent diagnostic tool at point of care as well as in resource limited settings. One study tested diagnostic accuracy of COVID-19 RAT tests from various manufacturers. The overall sensitivity of all fourteen RATs tested was 74.3% and the specificity was 100%. The more sensitive RAT tests are even considered to have the ability to identify contagious individuals[21].

Elevated levels of CRP, LDH, ferritin and procalcitonin significantly correlated with greater severity. Ferritin, however, did not correlate with the severity in 1st wave. The effect could be confounded by low Hb in severely ill patients and relatively smaller sample size. Procalcitonin was not significantly elevated in the 2nd wave, as it is raised only during the critical phase of COVID-19 infection. The timing of sample collection could have confounded the interpretation. Hence serial monitoring of laboratory markers may be needed.

The fetal complications could have been due to D614G mutation in the spike protein of newer variants that promotes interaction with host cell ACE2 receptors and associated escalated damage[22]. Similar rates of IUDs were also found in previous studies[16]. The adverse fetal outcome was significantly more in mothers with severe to critical disease for both waves (Table 5, Table 6).

Recent studies have shown that the severity of the disease significantly reduces with the administration of the COVID-19 vaccine. During the initial phase of the COVID-19 vaccination, the safety of these vaccines in pregnant women was not known. Hence, none of our patients had been vaccinated against COVID-19. The Federation of obstetrics and gynecology society India (FOGSI) has recently recommended it to be safe in this cohort[23]. Although various approved vaccines are in use and many are being developed, studies reporting efficacy of these vaccines in pregnant population are awaited. Until the pandemic is officially declared to have subsided, it is imperative that the 'new normal' life with COVID-19 appropriate behaviour is practiced diligently[24].

The immediate effects of COVID-19 on health care and particularly, obstetrics and gynaecology are readily evident. However, its long-term effects are predicted to unfold over months to years down the lane. COVID-19 infection itself is proposed to decrease birth rate by decrease conception, delaying further conception, and increase fetal loss. The socioeconomic impact of COVID-19 is catastrophic. Derailed cancer screening programmes during the pandemic is speculated to increase the number of gynaecological cancer patients presenting in advanced stage in the forthcoming years[24].

Observational single-center study design, lack of serial monitoring of laboratory parameters, and

COVID-19 testing in the neonate after 24-48 hours, confounding the vertical transmission, can all be the limitations of our study. However, the study has its distinctive features. Unlike previously published studies, our study has reported outcomes on the first and second waves. It was a prospective study and showed the correlation of the prognostic markers with the severity of maternal illness from the Indian population. The conclusions of this study would aid health care providers in better managing COVID-19 pregnancies in resource-poor settings by triaging the patients.

Conclusion

Our study showed that the clinical characteristics and severity of the disease did not differ significantly in both waves. The adverse fetal outcome was significantly more in mothers with severe to critical disease. Laboratory markers correlated significantly with the severity of the maternal disease; hence can be used as prognostic indicators.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395:809-15.
2 Sarkar A, Chakrabarti AK, Dutta S. Covid-19 infection in India: A comparative analysis of the second wave with the first wave. Pathogens 2021;10:1222-36.
3 Hassan N, Muzamil M, Banday D. COVID-19 infection during pregnancy - maternal and perinatal outcomes: a tertiary care centre study. Int J Reprod Contracept Obstet Gynecol 2020;9:3764-9.
4 Poon LC, Yang H, Kapur A, Melamed N, Dao B, Divakar H, et al. Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals. Int J Gynaecol Obstet 2020;149:273-86.
5 Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:3320-37.
6 Collin J, Byström E, Carnahan A, Ahrne M. Public health agency of sweden's brief report: pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand 2020,99:819-22.
7 Zhang C, Chu H, Pei YV, Zhang J. Laboratory effects of COVID-19 infection in pregnant women and their newborns: A systematic review and meta-analysis. Front Glob Womens Health 2021;2:647072.
8 Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. Crit Rev Clin Lab Sci 2020;57:415-31.
9 COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Retrieved June 30, 2021.
10 Waghmare R, Gajbhiye R, Mahajan NN, Modi D, Mukherjee S, Mahale SD. Universal screening identifies asymptomatic carriers of SARS-CoV-2 among pregnant women in India. Eur J Obstet Gynecol Reprod Biol 2021;256:503-5.
11 Bachani S, Arora R, Dabral A, Marwah S, Anand P, Reddy KS, et al. Clinical profile, viral load, maternal-fetal outcomes of pregnancy with COVID-19: 4-week retrospective, tertiary care single-centre descriptive study. J Obstet Gynaecol Can 2021;43:474-82.
12 Tadas MSP, Prashanthi S, Tankhiwale M, Singh M. Maternal COVID-19 infection, clinical characteristics, pregnancy and neonatal outcome: a prospective cohort study at a tertiary care center in Central India. Int J Res Med Sci 2021;9:1633-40.
13. Phupong V. Coronavirus disease-19 and pregnancy. Thai J Obstet Gynaecol 2020;28:66-70
14. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9:51-60.
15. Shah PT, Shah SR, Shah SR, Yadav PA, Patel BS, Chudasama TJ. Fetomaternal outcome in COVID-19 infected pregnant women: a preliminary clinical study. Int J Reprod Contracept Obstet Gynecol 2020;9:3704-10.
16 Nayak AH, Kapote DS, Fonseca M, Chavan N, Mayekar R, Sarmalkar M, et al. Impact of the coronavirus infection in pregnancy: a preliminary study of 141 patients. J Obstet Gynaecol India 2020;70:256-61.
17 Gajbhiye R, Modi D, Mahale S. Pregnancy outcomes, newborn complications and maternal-fetal transmission of SARS-CoV-2 in women with COVID-19: a systematic

review. med Rxiv 2020,10.1101/2020.04.11.20062356
18 Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacol Res 2020;157:104833.
19 Facchetti F, Bugatti M, Drera E, Lavazza A. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. EBioMedicine 2020;59:102951.
20 Hosier H, Farhadian SF, Morotti RA, Deshmukh U, Lu-Culligan A, Campbell KH, et al.: SARS-CoV-2 infection of the placenta . J Clin Invest 2020;130:4947-53.
21. Routsias JG, Mavrouli M, Tsoplou P, Dioikitopoulou K, Tsakris A. Diagnostic performance of rapid antigen tests (RATs) for SARS-CoV-2 and their efficacy in monitoring the infectiousness of COVID-19 patients. Sci Rep 2021;11:22863.
22 Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W et al.Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020;182:812-27.e19.
23 The Federation of Obstetric and Gynaecological Societies of India. FOGSI position statement COVID vaccination for pregnant & breastfeeding women; [Online] April 25, 2021. Accessed on September 24, 2021. https://www.fogsi.org/wp-content/uploads/covid19/fogsi-statement-on-covid-vaccination-in-pregnancy-and-bf.pdf
24 Vasuratna A, Manusirivithaya S, Tangjitgamol S. (Our) World with COVID-19. Thai J Obstet Gynaecol 2021;29: 122-30.

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GYNAECOLOGY

Female Sexual Dysfunction among Thai Women Using Hormonal Contraception versus Tubal Sterilization

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ABSTRACT

Objectives: Contraception is accepted worldwide by women to prevent unintended pregnancy. This study was aimed to evaluate female sexual function in women using hormonal contraception and tubal sterilization.

Materials and Methods: This was a cross-sectional study. Sexually active women 20-45 years old who used hormonal contraception or underwent tubal sterilization for at least 3 months were included. The participants self-completed the Thai version of the female sexual function index (FSFI) questionnaire to determine female sexual dysfunction (FSD) which consisted of six domains including sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction and pain. Demographic data were collected.

Results: A total of 310 women were recruited for this study. There were 155 participants who used hormonal contraception (79 used oral combined contraceptive pills, 56 used the depot medroxyprogesterone acetate (DMPA) and 20 used an implant) and 155 women underwent tubal sterilization. The prevalence of FSD was 70.9% and 64.5% in hormonal contraception group and tubal sterilization group. There was no statistically significant difference in the FSD between the groups ($p = 0.224$). The overall median FSFI score for hormonal contraception users was marginally and statistically significantly lower than tubal sterilization group ($p = 0.054$). Meanwhile, parity was the only significant associated factor that affected the FSD (adjusted odds ratio 3.32, 95% confidence interval 1.43 - 7.70).

Conclusion: The prevalence of FSD was high in both hormonal contraception users and the tubal sterilization group. Parity was the only significant associated factor that affected FSD.

Keywords: female sexual dysfunction, hormonal contraception, tubal sterilization.

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ผลของการคุมกำเนิดด้วยฮอร์โมนเปรียบเทียบกับการทำหมันหญิงที่มีต่อกิจกรรมทางเพศในสตรี

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บทคัดย่อ

วัตถุประสงค์: *การคุมกำเนิดเป็นที่ยอมรับทั่วโลกในการป้องกันการตั้งครรภ์ไม่พร้อม เพื่อศึกษาเปรียบเทียบกิจกรรมทางเพศของสตรีระหว่างการคุมกำเนิดด้วยฮอร์โมนและการทำหมัน*

วัสดุและวิธีการ: *เป็นการศึกษาแบบตัดขวาง ในผู้หญิงอายุ 20-45 ปี ที่การคุมกำเนิดด้วยฮอร์โมนหรือทำหมันเป็นระยะเวลาอย่างน้อย 3 เดือน อาสาสมัครจะได้ทำแบบสอบถามชนิดถามตอบเอง (Female Sexual Function Index questionnaire) เพื่อประเมินความบกพร่องทางเพศ ประกอบด้วย 6 หัวข้อหลัก คือ ความต้องการทางเพศ การกระตุ้นทางเพศ การหลั่งน้ำหล่อลื่น การถึงจุดสุดยอด ความพึงพอใจ และการเจ็บขณะมีการสอดใส่ และมีการเก็บข้อมูลส่วนตัว*

ผลการศึกษา: *อาสาสมัครทั้งหมดจำนวน 310 คน แบ่งเป็น 155 คน ใช้การคุมกำเนิดด้วยฮอร์โมน (79 รับประทานยาเม็ดคุมกำเนิด 56 คน ฉีดยาคุมกำเนิดและ 20 คน ฝังคุมกำเนิด) และ 155 คนทำหมัน พบว่าอัตราความชุกของการเกิดความบกพร่องทางเพศ คือ ร้อยละ 70.9 และร้อยละ 64.5 ในกลุ่มที่คุมกำเนิดด้วยฮอร์โมนและทำหมัน ตามลำดับ ซึ่งพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 0.224) ผลรวมค่าเฉลี่ยของคะแนน Female Sexual Function Index (FSFI) ในกลุ่มที่การคุมกำเนิดด้วยฮอร์โมนมีค่าน้อยกว่า เกือบจะแตกต่างกันอย่างมีนัยสำคัญทางสถิติ เมื่อเทียบกับกลุ่มที่ทำหมัน (p = 0.054) ในขณะที่จำนวนบุตรเป็นปัจจัยเดียวที่มีนัยสำคัญทางสถิติที่มีผลต่อความบกพร่องทางเพศ (adjusted odds ratio 3.32, 95% CI = 1.43 - 7.70)*

สรุป: *อัตราความชุกของการเกิดความบกพร่องทางเพศสูงทั้งในกลุ่มที่คุมกำเนิดด้วยฮอร์โมนและทำหมัน และจำนวนบุตรเป็นปัจจัยเดียวที่มีนัยสำคัญทางสถิติที่มีผลต่อความบกพร่องทางเพศ*

คำสำคัญ: *ความบกพร่องทางเพศ Female sexual function index, การคุมกำเนิดด้วยฮอร์โมน, การทำหมัน*

Introduction

The World Health Organization (WHO) has defined sexual health as the state of physical, emotional and social well-being with respect to sexuality[1]. Sexual life complexity is affected by many factors, that include medication and biological functions such as hormonal status, physical wellbeing, aging, and psychological health that in itself includes depression, anxiety, and self-image. Interpersonal factors that include relationship status and partner's sexual function plus sociocultural entities such as ethnicity, religion, and culture all may affect sexual health[2]. Although sexual dysfunction is not a threat to life, it affects the quality of life, marital status, self- esteem, and physical and emotional health.

The contraception method is one factor that has an effect on female sexuality[3, 4]. A study from Africa reported a strong association of hormonal contraception and female sexual dysfunction[4]. Although the benefit of contraception to prevent pregnancy outweighs the side effects such as nausea, dizziness, breast tenderness, vaginal spotting, these events might interfere with sexual relations. Currently, there are inconsistent data regarding the association between hormonal contraception and female sexual dysfunction (FSD)[5]. The effects range from negative to even positive[5-7]. Interestingly, many studies reported that non-hormonal contraception such as tubal sterilization is also a risk factor of FSD[8, 9]. One study reported the high prevalence of female dysfunction in Thai women using an intrauterine device[10]. Even though hormonal contraception and female sterilization are commonly used in Thailand, there was scarce evidence regarding sexual function related to contraceptive methods. Furthermore, sexual practices and perception are varied among women with different ethnicities[11, 12]. Thus, this study was aimed to evaluate female sexual function in women using hormonal contraception compared with those using tubal sterilization in Thai women.

Materials and Methods

This study was a cross-sectional study based on the female sexual function index (FSFI) questionnaire conducted between October 2019 and March 2020 at Srinagarind Hospital, Khon Kaen University, a tertiary care hospital in Khon Kaen, Thailand. Patients who came for an annual checkup at the gynecologic outpatient clinic were approached. The inclusion criteria were an age between 20-45 years old, who had used hormonal contraception (oral combined contraceptive pills, depot medroxyprogesterone acetate (DMPA), implant) or had undergone female sterilization at least 3 months previously, were sexually active within 4 weeks, and had no recent pelvic infection, abnormal pathology or underlying disease. The menopausal women, using emergency pills, and breast feeding women were excluded. Written informed consents were obtained.

FSD is defined as a disorder featuring the disturbance of orgasm, sexual Interest/arousal, and genito-pelvic pain[13].

To assess sexual function, the eligibility participants were approached and explained the questionnaire by a well-trained research assistant. All participants were asked to complete demographic data and a validated FSFI questionnaire (Thai version) in a private room which took about 10 minutes to complete the questionnaire.

FSFI is a questionnaire specifically designed and validated for evaluating female sexual function. The questionnaire consists of six domains, 19 items, including sexual desire (2 questions), sexual arousal (4 questions), lubrication (4 question), orgasm (3 questions), sexual satisfaction (3 questions) and pain during sexual intercourse (3 questions). Each item score ranged from 0 - 5 except for items 1, 2, 15 and 16, each of which had the range between 1 and 5. Factors were 0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction and pain. The total score was obtained by adding the six domain scores (full score 36). The higher scores indicating better function in each domain. The total score of less than 26.55 was determined as FSD[14]. The FSFI questionnaire has been translated and validated in many countries. In this study, the Thai version of the FSFI questionnaire translated by the Mapi Research Trust was used.

The study was approved by the institutional review board of the Khon Kaen University Ethics Committee on Human Research (HE621338).

Based on Kunkeri 's study[16], the prevalence of FSD after tubal sterilization was 71.7%. In this study, it was assumed that 20% better in hormonal contraception users. In order to achieve a power of 80% and a level of significance of 5%, at least 143 participants were needed in each group. Incomplete data were added as 10%.

Statistical analysis

Data analysis was performed by the STATA program version 10.1. Categorical data were reported in number and percentage. Continuous data were shown in mean ± standard deviation (SD) or median and interquartile range (IQR). Associated factors that affected sexual function were reported as a percentage by using the Pearson Chi-square test. FSFI domain and total scores were calculated and reported as the median and IQR and the Kruskal-Wallis test was used with non-normal distribution of data. Multivariate logistic regression analysis was performed to compare the associations between dependent and independent variables. The p value < 0.05 was considered to be statistically significant.

Results

During the enrollment period, 393 eligible women were approached and 83 women refused to complete the FSFI questionnaire. Three- hundred and ten women were recruited for this study. One hundred fifty-five participants used hormonal contraception (79 used an oral combined contraceptive pills-OCP, 56 used DMPA and 20 used implants) and 155 women had undergone tubal sterilization. The mean age of the hormonal contraception group was significantly lower than the tubal sterilization group (32.9 ± 6.9 vs 38.3 ± 4.7, p < 0.001). Baseline characteristics of participants using hormonal contraception or tubal sterilization are shown in Table 1.

Table 1. Baseline characteristics of participants (n = 310).

Parameters	Hormonal contraception (n = 155)	Tubal sterilization (n = 155)	p value
Age (years)	32.9 ± 6.9	38.3 ± 4.7	< 0.001
20 - 35	94 (60.6)	40 (25.8)	
36 - 45	61 (39.4)	115 (74.2)	
Duration of use (years)			< 0.001
< 1	52 (33.5)	9 (5.8)	
1-5	60 (38.7)	50 (32.3)	
> 5	43 (27.7)	96 (61.9)	
BMI (kg/m^2)	22.9 ± 4.3	23.5 ± 4.1	0.516
< 18.5	15 (9.7)	14 (9)	
18.5 - 22.9	75 (48.4)	66 (42.6)	
> 23	65 (41.9)	75 (48.4)	
Parity			< 0.001
none	41 (26.5)	0 (0)	
1	78 (50.3)	7 (4.5)	
> 1	36 (23.2)	148 (95.5)	

Table 1. Baseline characteristics of participants (n = 310). (Cont.)

Parameters	Hormonal contraception (n = 155)	Tubal sterilization (n = 155)	p value
Route of delivery			< 0.001
Vaginal delivery	69 (44.5)	85 (54.8)	
Cesarean delivery	41 (26.5)	49 (31.6)	
Both	5 (3.2)	21 (13.5)	
Never	40 (25.8)	0 (0)	
Occupation			0.239
Government	79 (50.9)	77 (49.7)	
Private employee and others	54 (34.8)	65 (41.9)	
Housewife	22 (14.2)	13 (8.4)	
Income (Baht/month)			0.971
< 10,000	17 (10.9)	17 (10.9)	
10,000 - 30,000	72 (46.5)	70 (45.2)	
> 30,000	66 (42.6)	68 (43.9)	
Educational level			0.001
Primary school	4 (2.6)	18 (11.6)	
Secondary school	68 (43.9)	78 (50.3)	
Bachelor degree and above	83 (53.5)	59 (38)	

Data are presented as mean ± standard deviation and number (percentage)
BMI: body mass index

Overall, the prevalence of FSD was 67.7%. The prevalence of FSD was higher in the hormonal contraception group compared to the tubal sterilization group (64.5% vs. 70.9%). The differences between both groups, however, did not reach statistical significance (p = 0.224) (Table 2).

Table 2. Associating factors affected female sexual function (n = 310).

Parameters	n	Female sexual dysfunction (%)	p value
Type of contraception			0.224
Hormonal contraception	155	110 (70.9)	
Tubal sterilization	155	100 (64.5)	
Age (years)			0.956
20 - 35	134	91 (67.9)	
36 - 45	176	119 (67.6)	
Duration of use (years)			0.248
< 1	61	44 (72.1)	
1-5	110	68 (61.8)	
> 5	139	98 (70.5)	

Table 2. Associating factors affected female sexual function (n = 310). (Cont.)

Parameters	n	Female sexual dysfunction (%)	p value
BMI (kg/m^2)			0.005
< 18.5	29	13 (44.8)	
18.5 - 22.9	141	92 (65.2)	
> 23	140	105 (75)	
Parity			0.002
none	41	23 (56)	
1	85	70 (82.3)	
BMI (kg/m^2)			0.005
< 18.5	29	13 (44.8)	
18.5 - 22.9	141	92 (65.2)	
> 23	140	105 (75)	
Parity			0.002
none	41	23 (56)	
1	85	70 (82.3)	
> 1	184	117 (63.5)	
Route of delivery			0.088
Vaginal delivery	154	102 (66.2)	
Cesarean delivery	89	67 (75.2)	
Both	26	19 (73)	
Never	41	22 (53.6)	
Occupation			0.395
Government	156	99 (63.4)	
Private employee and others	120	87 (72.5)	
Housewife	34	24 (70.5)	
Income (Baht/month)			0.730
< 10,000	34	25 (73.5)	
10,000 - 30,000	142	96 (67.6)	
> 30,000	134	89 (66.4)	
Education level			0.445
Primary school	22	17 (77.2)	
Secondary school	146	101 (69.1)	
Bachelor degree and above	142	92 (64.7)	

BMI: body mass index

The hormonal contraception users had lower FSFI scores in all aspects especially in desire domain (p = 0.035) (Table 3). The overall median FSFI score in the hormonal contraception users was marginally statistically significantly lower than the tubal sterilization group (p = 0.054) (Table 3).

Table 3. Female Sexual Function Index score in hormonal contraception and tubal sterilization group.

Domain	Hormonal contraception (n = 155)	Tubal sterilization (n = 155)	p value
Desire	3 (2.4, 3.6)	3.6 (3, 3.6)	0.035*
Arousal	3.6 (2.7, 3.9)	3.6 (3, 3.9)	0.061
Lubrication	4.2 (3.6, 4.8)	4.2 (3.6, 5.1)	0.286
Orgasm	4.4 (3.6, 4.8)	4.4 (3.6, 5.2)	0.14
Satisfaction	4.8 (3.6, 5.2)	4.8 (3.6, 5.2)	0.438
Pain	4.4 (3.6, 4.8)	4.4 (3.6, 5.2)	0.149
Total score	23.6 (19.6, 27.1)	25 (21.4, 28)	0.054

Data are presented as median (interquartile range). * Kruskal-Wallis test

When the hormonal contraception users were classified into type and route of administration, the lowest FSFI score was found in the implant group (median = 20.05, IQR = 19-26) (Table 4).

Table 4. Female sexual function index score in difference type and root of administration of hormonal contraception.

Domain	Oral combined pill (n = 79)	DMPA (n = 56)	Implant (n = 20)
Desire	3 (2.4, 3.6)	3 (2.4, 3.6)	3 (2.1, 3.6)
Arousal	3.6 (3, 3.9)	3.6 (2.7, 3.75)	3 (2.4, 3.6)
Lubrication	3.6 (3.6, 4.8)	4.2 (3.6, 4.8)	4.2 (3.3, 4.65)
Orgasm	3.6 (3.6, 5.2)	4.4 (3.6, 4.8)	4 (3, 4.6)
Satisfaction	4.2 (3.6, 5.2)	4.8 (3.6, 4.8)	4.8 (3.4, 5.4)
Pain	4 (3.6, 4.8)	4.4 (3.6, 4.8)	4.4 (3.6, 5)
Total score	23.9 (20.7, 27.4)	23.6 (19.3, 26.3)	20.05 (19, 26)

Data are presented as median (interquartile range)

Associated factors that affected FSD, body mass index (BMI) and parity had a statistically significant association (Table 2). When a multivariate logistic regression model was conducted, parity was the only factor that remained significantly associated with FSD (adjusted odds ratio 3.32, 95% confidence interval (CI) 1.43 - 7.70) (Table 5). Age was considered to be an important confounder. Although the difference was not significant (Table 5), we included this factor into the logistic regression model. Furthermore, we also reclassified the parity in this analysis. The results, however, did not change (adjusted odds ratio 3.37, 95%CI 1.44 - 7.88).

Table 5. Multivariate logistic regression modeling predicting female sexual dysfunction.

Parameter	Adjusted odds ratio	95% confidence interval
Type of contraception		
Hormonal contraception	reference	reference
Tubal sterilization	0.96	0.47 - 1.96
BMI (kg/m^2)		
18.5 - 22.9	reference	reference
< 18.5	0.50	0.22 - 1.15
> 23	1.64	0.97 - 2.79
Parity		
none	reference	reference
1	3.32	1.43 - 7.70
> 1	1.28	0.53 - 3.13

BMI: body mass index

Discussion

The prevalence of FSD among women using hormonal contraception or who underwent tubal sterilization was very high. Approximately two-thirds of both groups had FSD. The median FSFI score of all domains in the hormonal contraception user group was marginally statistically significantly lower than tubal sterilization group. The possible explanation is that hormonal contraception causes female sexual function that includes: 1) increased levels of sex hormone-binding globulin (SHBG)[5]. High SHBG serum levels can reduce free testosterone levels since testosterone has a high affinity for SHBG[17], 2) suppressed ovarian production of androgen is linked to vaginal dryness and decreased lubrication[7,17], 3) oral hormonal contraceptives produce side effects (headache, dizziness, vaginal spotting). These factors could decrease sexual arousal, sexual satisfaction, orgasm frequency and cause increased sexual pain[4]. Interestingly, the prevalence of FSD in the hormonal contraception group in this study was two times higher than the results from a study of European women using OCP[18]. A systematic review in 2013 also revealed that ethnicity is able to modulate the risk of sexual dysfunction[19]. A higher prevalence of FSD was observed in Southeast Asian women than in other global regions. The belief in that religion guides sex and culture may play an important role in the negative impact on sexual problems in Asian populations[2, 20].

The prevalence of FSD was 64.5% in the tubal sterilization group. This finding was lower than the recent report from India in which FSD was found to be in 71.1% of women who had undergone sterilization[16]. The psychological impact, such as post-sterilization regret, was proposed to be the explanation in those with sexual function decline[5]. Furthermore, the decrease in ovarian blood flow from dissecting of the ovarian branch of uterine artery during sterilization could result in hormonal changes[8]. The study from a western country, however, demonstrated no change or even a positive effect[3].

The median FSFI scores of all domains were

comparable among all types of contraception. Implants users reported the lowest total scores. A recent cross-sectional study from the Contraceptive CHOICE Project showed an increased odds of decreased sexual interest in implant users (adjusted OR 1.60, 95%CI 1.03-2.49)[21]. A study from Italy, however, showed a slow yet increased positive impact on sexual life[22]. This inconclusive effect needs a further well-designed study to be elucidated.

For the associated factors, the type of contraception, BMI, and parity were included in the multivariate model of FSD that seemed to increase with increasing BMI. The association did not reach a significant level in this study. On the contrary, a study in Thai women using IUDs showed that FSD was mainly affected in underweight women[10]. Concern about body image and low self-esteem are the plausible explanations for the influence of abnormal weight in both ways on sexual function. Parity was the only significant associated factor that affected FSD in this analysis. Latest evidence indicated that sexual activity was infrequent and more problematic among primiparous lactating women compared to multiparous women[23]. Conversely, parity was reported to be associated with FSD in a study from Bangladesh (adjusted OR 3.4, 95%CI 1.21-9.68)[24]. A long term effect of parity on sexual function has not been well understood.

To the authors' knowledge, this study is the first study comparing sexual function in women using hormonal contraception and tubal sterilization, however, the present study also had some limitations. This study was unable to establish a causal link between contraceptive methods and sexual dysfunction. Many confounding factors were unable to evaluate including type of progestin in hormonal contraception, compliance, duration after delivery, frequency of sexual relations, relationship status and partner's sexual function. A prospective study to measure the effect of contraception on the change in sexual function would be beneficial. Although the prevalence of FSD might be higher in an Asian population, the proportion found in this study was still exceptionally high in both groups. The difference of sexual function between the methods of interest could be masked. Nevertheless, sexual function assessment should be incorporated in family planning services because of the possible sequelae of contraceptive methods. Exercising, intimate communication and sex education, the protective factors of FSD, should be addressed and empowered by healthcare personnel[25]. If applicable, women with severe FSD should be referred to specialist.

Conclusions

The prevalence of female sexual dysfunction was high in both hormonal contraception users and the tubal sterilization group. Although female sexuality is very complex, sexual function assessment should be incorporated as a part of the counselling process to provide optimum care.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. Sexual health and its linkages to reproductive health: an operational approach. Geneva, Switzerland 2017.
2. Althof SE, Leiblum SR, Chevret-Measson M, Hartmann U, Levine SB, McCabe M, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. J Sex Med 2005;2:793-800.
3. Costello C, Hillis SD, Marchbanks PA, Jamieson DJ, Peterson HB, US Collaborative Review of Sterilization Working Group. The effect of interval tubal sterilization on sexual interest and pleasure. Obstet Gynecol 2002;100:511-7.
4. Butt MR, Lema V, Mukaindo A, Mohamoud G, Shabani J. Prevalence of and factors associated with female sexual dysfunction among women using hormonal and non-hormonal contraception at the AGA Khan

University Hospital Nairobi. Afr J Prim Health Care Fam Med 2019;11:e1-9.
5. Casey PM, MacLaughlin KL, Faubion SS. Impact of contraception on female sexual function. J Women Health 2017;26:207-13.
6. Ertekin Pinar S, Demirel G, Yildirim G, Daglar G. Sexual experiences and quality of life in Turkish women using methods of contraception. J Obstet Gynaecol 2019;39:782-7.
7. Smith NK, Jozkowski KN, Sanders SA. Hormonal contraception and female pain, orgasm and sexual pleasure. J Sex Med 2014;11:462-70.
8. Gulum M, Yeni E, Sahin MA, Savas M, Ciftci H. Sexual functions and quality of life in women with tubal sterilization. Int J Impot Res 2010;22:267-71.
9. Sadatmahalleh SJ, Ziaei S, Kazemnejad A, Mohamadi E. Evaluation of sexual function and quality of life in Iranian women with tubal ligation: a historical cohort study. Int J Impot Res 2015;27:173-7.
10. Panchalee T, Wongwananuruk T, Augsuwatana S, Sirimai K, Tammakunto M, Neangton C, et al. Prevalence and associating factors of sexual dysfunction in women who use intrauterine device (IUD) for contraception. J Med Assoc Thai 2014;97:20-7.
11. Cain VS, Johannes CB, Avis NE, Mohr B, Schocken M, Skurnick J, et al. Sexual functioning and practices in a multi-ethnic study of midlife women: baseline results from SWAN. J Sex Res 2003;40:266-76.
12. Meston CM, Ahrold T. Ethnic, gender, and acculturation influences on sexual behaviors. Arch Sex Behav 2010;39:179-89.
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorder: DSM-5. Washington DC 2013.
14. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1-20.
15. FSFI-Female sexual function index [Internet]. http://eprovide.mapi-trust.org/instruments/female-sexual function index. [cited 2000 Feb 17]. Available from: http://eprovide.mapi-trust.org/instruments/female-sexual function index
16. Kunkeri SP, Sathyanarayana Rao TS, Andrade C. Study of sexual functioning and disorder in women before and after tubal sterilization (tubectomy). Indian J Psychiatry 2017;59:63-8.
17. Both S, Lew-Starowicz M, Luria M, Sartorius G, Maseroli E, Tripodi F, et al. Hormonal contraception and female sexuality: Position Statements from the European Society of Sexual Medicine (ESSM). J Sex Med 2019;16:1681-95.
18. Wallwiener CW, Wallwiener L-M, Seeger H, Schönfisch B, Mueck AO, Bitzer J, et al. Are hormonal components of oral contraceptives associated with impaired female sexual function? A questionnaire-based online survey of medical students in Germany, Austria, and Switzerland. Arch Gynecol Obstet 2015;292:883-90.
19. Lewis RW. A critical look at descriptive epidemiology of sexual dysfunction in Asia compared to the rest of the world - a call for evidence-based data. Transl Androl Urol 2013;2:54-60.
20. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, et al. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 2005;17:39-57.
21. Boozalis A, Tutlam NT, Chrisman Robbins C, Peipert JF. Sexual desire and hormonal contraception. Obstet Gynecol 2016;127:563-72.
22. Guida M, Cibarelli F, Troisi J, Gallo A, Palumbo AR, Di Spiezio Sardo A. Sexual life impact evaluation of different hormonal contraceptives on the basis of their methods of administration. Arch Gynecol Obstet 2014;290:1239-47.
23. Banaei M, Alidost F, Ghasemi E, Dashti S. A comparison of sexual function in primiparous and multiparous women. J Obstet Gynaecol 2020;40:411-8.
24. Jahan MS, Billah SMB, Furuya H, Watanabe T. Female sexual dysfunction: facts and factors among gynecology outpatients. J Obstet Gynaecol Res 2012;38:329-35.
25. McCool-Myers M, Theurich M, Zuelke A, Knuettel H, Apfelbacher C. Predictors of female sexual dysfunction: a systematic review and qualitative analysis through gender inequality paradigms. BMC Women Health 2018 22;18:108.
26. Pacific WHORO for the W. The Asia-Pacific perspective: redefining obesity and its treatment [Internet]. Sydney : Health Communications Australia; 2000 [cited 2020 Oct 29].

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OBSTETRICS

Impact of Time since Last Meal on the False Positive Result of 50 grams Glucose Challenge Test in the Pregnancy with Gestational Diabetes Mellitus Risk: A prospective cohort study

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ABSTRACT

Objectives: To study the impact of time since last meal to the rate of false positive 50 grams glucose challenge test (GCT) during pregnancy with gestational diabetes mellitus (GDM) risk.

Materials and Methods: This prospective observational study was conducted in a tertiary care from December 2019 to August 2020. The participants were the singleton who had risks of GDM. The screening test was done using 50 grams GCT and then 100 grams oral glucose tolerance test (OGTT) used for diagnosis of GDM if GCT was ≥ 140 mg/dL. The participants' information, time and type of last meal, time of 50 grams glucose intake and blood drawing, result of GCT and OGTT were recorded. The time since last meal was categorized to < 1, < 2 and < 3 hours. Bivariate and multivariable regression analysis were applied to evaluate the effect of time since last meal to GCT.

Results: There were 426 pregnant women completed study: 30.75% had positive GCT and 19% of these were diagnosis for GDM. The time since last meal < 1, < 2, and < 3 hours group had 36.0, 29.8, and 25.8 % false-positive CGT compared with 20.8, 18.2, 20.3% of ≥ 1, ≥ 2, and ≥ 3 hours group. The adjusted risk ratio (95% confidence interval) were 1.60 (1.14-2.24), 1.53 (1.06-2.22) and 1.23 (0.75-2.04) and p value were 0.006, 0.023, and 0.397, respectively.

Conclusion: The interval between the last meal and GCT less than 2 hours significantly increased a false positive rate of the test.

Keywords: false-positive, glucose challenge test, gestational diabetes mellitus, last meal intake.

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ผลกระทบของระยะเวลาหลังอาหารมื้อสุดท้ายกับการเกิดผลบวกลวงจากการตรวจคัดกรองเบาหวานระหว่างตั้งครรภ์

ศุภวรรณ ปัทมธรรมกุล, ศรีสุดา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์, อังคณา หารศรี, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลกระทบของระยะเวลาหลังอาหารมื้อสุดท้ายก่อนตรวจคัดกรองเบาหวาน 50 กรัม glucose challenge testในสตรีตั้งครรภ์ที่มีความเสี่ยงเบาหวานต่อการเกิดผลบวกลวง*

วัสดุและวิธีการ: *งานวิจัยแบบศึกษาไปข้างหน้าในสถานพยาบาลตติยภูมิตั้งแต่ธันวาคม 2562 ถึง สิงหาคม 2563 โดยทำการศึกษาในสตรีตั้งครรภ์เดี่ยวที่มีความเสี่ยงในการเกิดภาวะเบาหวานระหว่างตั้งครรภ์ที่มาฝากครรภ์และได้รับการตรวจด้วยการคัดกรองด้วยวิธี 50 g GCT หากผลตรวจคัดกรองผิดปกติ (≥ 140 mg%) จะได้รับการตรวจวินิจฉัยภาวะเบาหวานด้วยวิธี 100g oral glucose tolerance test (OGTT) โดยการซักประวัติมารดาที่เข้าร่วมงานวิจัยเกี่ยวกับข้อมูลทั่วไป เวลาที่รับประทานมื้อสุดท้าย ชนิดและปริมาณของอาหารที่รับประทาน เวลาที่ได้รับการกลืนน้ำตาลและเวลาที่ได้รับการเจาะเลือด โดยระยะเวลาหลังอาหารมื้อสุดท้ายจะแบ่งเป็น < 1, < 2 และ < 3 ชั่วโมง ผลลัพธ์ของการตรวจจะถูกบันทึกและนำมาวิเคราะห์เพื่อหาผลกระทบและความสัมพันธ์ของระยะเวลาหลังอาหารมื้อสุดท้ายต่อระดับน้ำตาลและผลบวกลวงโดยใช้การคำนวณทางสถิติ bivariate and multivariable regression*

ผลการศึกษา: *สตรีตั้งครรภ์ที่เข้าร่วมงานวิจัยทั้งหมด 426 คน มีร้อยละ 30.75 ที่ตรวจคัดกรองได้ผลผิดปกติ ในกลุ่มนี้พบว่าร้อยละ 19 ได้รับวินิจฉัยภาวะเบาหวาน และเมื่อเปรียบเทียบความสัมพันธ์ของระยะเวลาจากอาหารมื้อสุดท้ายก่อนได้รับการตรวจคัดกรองเบาหวานพบว่าที่เวลา < 1,< 2 และ < 3 ชั่วโมง มีผลบวกลวงจากการตรวจร้อยละ 36.0, 29.8 และ 25.8 เทียบกับที่เวลา ≥ 1, ≥ 2 และ ≥ 3 ชั่วโมงที่มีผลบวกลวงร้อยละ 20.8, 18.2 และ 20.3 ตามลำดับ จากการวิเคราะห์แบบ multivariable regression analysis พบว่ามีค่า adjusted risk ratio 1.60 (1.14-2.24), 1.53 (1.06-2.22) และ 1.23 (0.75-2.04), มีค่า p value เท่ากับ 0.006, 0.023, and 0.397 ตามลำดับ*

สรุป: *ช่วงเวลาหลังอาหารมื้อสุดท้ายมีผลต่อตรวจต่อการคัดกรองเบาหวาน GCT พบว่าที่เวลาน้อยกว่าสองชั่วโมงเป็นต้นไปทำให้เพิ่มผลบวกลวงของการตรวจคัดกรองเบาหวานอย่างมีนัยสำคัญทางสถิติ*

คำสำคัญ: *ผลบวกลวง, การคัดกรองเบาหวาน, ภาวะเบาหวานขณะตั้งครรภ์, มื้ออาหาร*

Introduction

Gestational diabetes mellitus (GDM) is a common problem that effects both maternal and fetal health during pregnancy. The effects include increased risk of fetal macrosomia, fetal anomaly, shoulder dystocia, cesarean delivery rate, fetal death and further overt DM in both the mother and the newborn[1, 2]. In Thailand, the prevalence rate of GDM is reported as between 1.5-9.3%[3-7] compared with a prevalence rate in the United State of 9.2%[8].

There is no consensus on a standard GDM diagnostic tools and this has had an effect to the variation in diagnosis criteria, screening and management by different medical centers[9-12]. Two-step approach for diagnosis of GDM, consists of a 1 hour 50 grams glucose challenge test (GCT) followed by a 100 grams oral glucose tolerance test (OGTT). This method is recommended by the American College of Obstricians and Gynecologists (ACOG)[1] and has been widely used in many medical centers in Thailand.

A false-positve GCT is definded as the patient has a positive GCT but a negative OGTT. The false-positive GCT result is inconvenient for the patients, increases cost of screening, which can cause additional unnecessary diagnostic test, treatment and increased maternal concern about their health condition[13]. The significance of this false-positive group is questionable, there are some studies that considered the false-positive GCT as an early form of glucose intolerance[14-16] and effect to perinatal outcomes[17-20].

Recently, there have been some studies on the impact of meal timing and calories and their influence on glucose levels in adults[21-24]. There are a few studies that investigated the effect of timing, fasting duration and calories on glucose levels following GCT screening in pregnant woman which might effect the false-positive screening GCT[25-28]. There was neither a practical cut-off point since last meal nor calories were tested for application on the GCT. Thus, the primary objective of this study was to investigate the influence of last meal timing on GDM screening result. The secondary objective was to evaluate the effect of calories of last meal on the GCT result. The aim was to create practical patient advise for at risk patients who were undergoing GCT screening.

Materials and Methods

This prospective cohort study was conducted at the antenatal care (ANC) clinic, Udonthani Hospital, Udonthani, Thailand, from December 2019 to August 2020. The study protocol was approved by Human Research Ethical Committee of Udonthani Hospital (No.62/2562). All participants were counselled and gave their consent before participating in this study.

The inclusion criteria were all singleton pregnant women, who had risk for GDM according to the hospital's protocol including: maternal age ≥ 35 years at expected date of delivery, pre-pregnancy weight ≥ 70 kg or BMI > 30 kg/m^2, family member with DM, previous GDM, previous fetal macrosomia (> 4,000 g), previous unknown cause of intrauterine fetal death, previous child with shoulder dystocia, history of impaired blood glucose and glucosuria > 2$^+$ at least 2 times. This inclusion criteria were the Udonthani Hospital's protocol which applied from Royal Thai College of Obstetricians and Gynecologists and Srinagarind Hospital GDM guideline practice[29, 30]. The exclusion criteria were (1) known case of overt DM, (2) pregnant woman who had positive GCT, but did not receive 100 g OGTT confirmation, (3) unwilling to participate with this study. The screening test was conducted at first time ANC and repeat at 24-28 gestational age if negative result for first time screening.

All participants were asked for their: characteristics, risk of GDM factors as inclusion criteria protocols, time, and type of last meal intake. The time of glucose ingestion and blood drawing for glucose test were collected by nurses who were counselled the method to collect data at the ANC clinic. The time, since last meal until glucose intake, was divided into two groups: group 1 (less than 2 hours) and group 2 (equal to or more than 2 hours)[25, 26]. The calories were evaluated by calories table of Thai public health department and type of meal was divided into light (< 300 calories) and heavy meal (≥ 300 calories)[31]. Blood glucose at 1 hour after 50 grams glucose intake was measured.

Two step approach was applied to test in pregnant woman who had risks for GDM were performed a 50 grams GCT without starvation and venous plasma

glucose was measured at 1 hour after ingestion. All The positive GCT test was the blood glucose at 1 hour after 50 grams glucose intake ≥ 140 mg/dl. The confirmatory test by 100 grams OGTT was done within one week. The positive OGTT test was defined as at least 2 values of blood glucose levels at fasting, 1, 2, and 3 hours after 100 grams glucose intake were ≥ 105, 190, 165, 145 mg/dl, respectively according to the National Diabetes Data Group (NDDG) criteria[1]. The false positive GCT test was defined as the positive result of GCT (GCT ≥ 140 mg/dl) with negative result of 100 grams OGTT by NDDG criteria. The blood glucose was tested by hexokinase technique (Achitech 46000 machine, Abbott Laboratories Company).

Statistical analysis

The sample size was calculated by Stata statistical program using formula for Chi-squared test comparing two independent proportions. The proportion of false positive GCT in time since last meal equal to or more than 2 hours group (control) and less than 2 hours group from pilot study in our center were 0.15 and 0.30. The 0.01 significance level was used. The calculated sample size was 180 per group. The estimated prevalence of potential risk for GDM in our center was 30%. Therefore, the estimated time for collection of cases at ANC clinic was nine months, all cases, which compatible with the inclusion criteria between the study period, were collected.

The participants' characteristics were presented in term of number, percentage, mean and standard deviation. The comparison of factors between two groups was calculated by Pearson's chi square, Fisher exact or student t test depending on the characteristic of variables. The crude and adjusted risk ratio with 95% confidence interval were calculated by bivariable and multivariable regression analysis. The p value < 0.2 was used for selecting variable to multivariable analysis and p value < 0.05 was used for statistically significance. All analyses were performed using Stata Release 13 statistical software (Stata Corp, College Station, TX).

Results

There were 443 participants who meet the inclusion criteria for GDM screening from December 2019 to August 2020. There were 17 participants who were excluded: 2 were overt DM, 2 were unwilling to participate in this study and 13 were unobtainable to confirm diagnostic test (Fig. 1). The total number of participants was 426 which were divided into 2 group by timing from last meal to ingesting 50 grams glucose. These two groups were: group 1 (last meal intake time less than 2 hours) and group 2 (last meal intake equal to or more than 2 hours). The number of participants were 245 and 181 respectively. Mean age ± standard deviation (SD) of all participants was 27.5 ± 6.6 years and the mean BMI ± SD was 24.5 ± 5.8. Mean gestational age was 21.4 weeks and other data are presented in Table 1. There were no significant different of epidemiological characteristics in both groups.

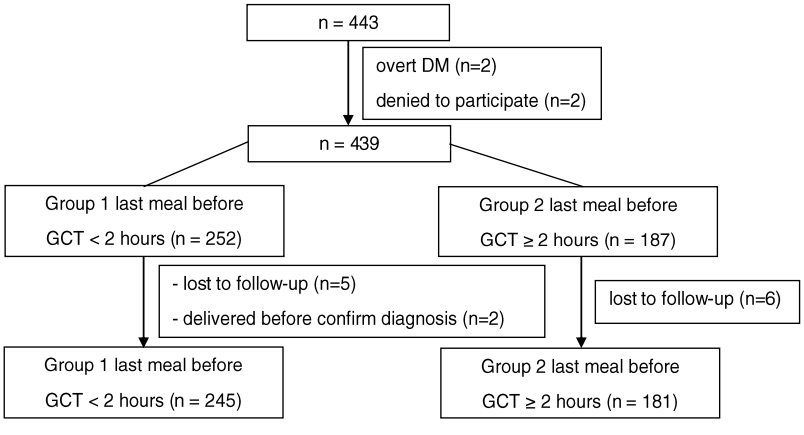

Fig. 1. Flow diagram of identification process for this study.

Table 1. Comparison of epidemiological characteristics between group 1(time since last meal less than 2 hours) and group 2 (time since last meal equal to or more than 2 hours).

Characteristics	Total (n = 426)	Group 1 (n = 245)	Group 2 (n = 181)	p value
Age (years)	27.5 ± 6.6	27.8 ± 6.8	27.1 ± 6.3	0.31
Primigravida, n (%)	158 (37.1%)	87 (35.5%)	68 (37.6%)	0.676
Gestational age (weeks)	21.4 ± 9.7	21.6 ± 9.5	21.2 ± 9.9	0.694
Weight (kgs)	61.8 ± 14.6	61.9 ± 14.1	61.6 ± 15.3	0.813
BMI (kgs/m^2)	24.5 ± 5.8	24.5 ± 5.5	24.5 ± 6.1	0.741
Category (n, %)				0.408
< 18.5	43 (10.1%)	20 (8.1%)	23 (12.7%)	
18.5 to < 25	221 (51.8%)	131 (53.5%)	90 (49.7%)	
25 to < 30	100 (23.5%)	59 (24.1%)	41 (22.6%)	
30 to < 40	56 (13.2%)	33 (13.5%)	23 (12.7%)	
≥ 40	6 (1.4%)	2 (0.8%)	4 (2.2%)	
Underlying disease				0.31
Hypertension	8 (1.9%)	2 (0.8%)	6 (3.3%)	
Hyperthyroid	4 (0.9%)	3 (1.2%)	1 (0.6%)	
SLE	3 (0.7%)	1 (0.4%)	2 (1.1%)	
Occupation				0.723
Housewife	212 (49.7%)	126 (51.4%)	86 (47.5%)	
Employee	130 (30.5%)	70 (28.5%)	60 (33.2%)	
Marchant	44 (10.3%)	26 (10.7%)	18 (9.9%)	
Government worker	37 (8.9%)	22 (8.9%)	15 (8.3%)	
Other	3 (0.7%)	1 (0.4%)	2 (1.1%)	
Relatives				0.6
First degree relatives	105 (24.6%)	65 (26.5%)	40 (22.1%)	
Second degree relatives	159 (37.3%)	96 (39.1%)	63 (34.8%)	
Previous pregnancy				0.597
Fetal macrosomia	5 (1.2%)	1 (0.4%)	4 (2.2%)	
Fetal anomalies	5 (1.2%)	3 (1.2%)	2 (1.1%)	
Previous GDM	4 (0.9%)	2 (0.8%)	2 (1.1%)	
Preeclampsia	3 (0.7%)	2 (0.8%)	1 (0.6%)	

Data are presented as mean ± standard deviation unless specified otherwise.
BMI: Body Mass Index, SLE: Systemic Lupus Erythematosus, GDM: Gestational Diabetes Mellitus

Fig. 2 and Table 2 demonstrate the primary outcome of this study. The mean of 50 g GCT of all participants was 127.4 mg/dl and 131 participants (30.8%) were GCT positive when used the cut-off point at 140 mg/dl (41.3% when used the cut-off at 130 mg/dl). There was 19.0% form this group had positive for diagnostic test by using NDDG criteria (26.7% using Carpenter's criteria), meanwhile prevalence of GDM in at risk group from this study was 5.8% (8.2% using Carpenter's criteria).

The positive OGTT (GDM) prevalence was higher in group 2 (time since last meal equal to or more than

2 hours). The GCT false positive was 106 participants from the total GCT screening (24.9%) which was higher in group 1 (time since last meal less than 2 hours) with statistical significance. The power of study calculated by number of participants and proportion of false positive cases was 0.83 with the alpha error at 0.05.

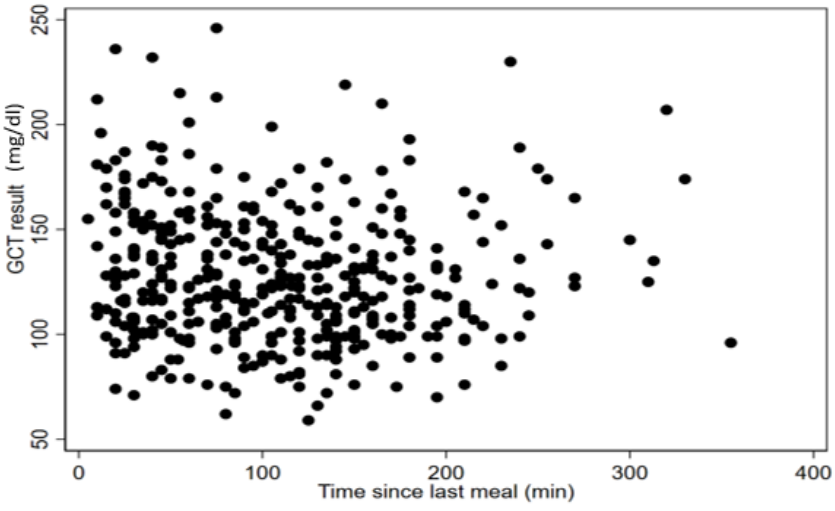

Fig. 2. Distribution of time since last meal (minutes) and 50 grams glucose challenge test (GCT) result (mg/dl).

Table 2. Result of GCT and OGTT between group 1 (time since last meal less than 2 hours) and group 2 (time since last meal equal to or more than 2 hours).

Results	Total (n = 426)	Group 1 (n = 245)	Group 2 (n = 181)	p value
50 grams GCT, mean ± SD (95%CI)	127.4 ± 31.7 mg/dl (124.4-130.4)	130.2 ± 31.9 mg/dl (126.1-134.2)	123.6 ± 31.1 mg/dl (119.1-128.2)	0.033
Positive GCT, n (%)	131 (30.8%)	85 (34.7%)	46 (25.4%)	0.040
Positive OGTT (GDM), n (%)	25/131 (19.1%)	12/85 (14.1%)	13/46 (28.3%)	0.049
False positive GCT/total GCT	106/426 (24.9%)	73/245 (29.8%)	33/181 (18.2%)	0.006

GCT: glucose challenge test, OGTT: oral glucose tolerance test, SD: standard deviation, CI: confidence interval, GDM: Gestational Diabetes Mellitus

The comparison of false positive GCT to various time since last meal and calories were presented in Table 3. The time since last meal of less than 1 and 2 hours had an effect to a false positive GCT with a risk ratio (RR) 1.72 (1.42-2.86) and 1.63 (1.13-2.35), respectively while 3 hours since last meal had no significant difference for false positive GCT with RR 1.27 (0.77-2.09). The mean calories of last meal intake were 389.8 kcal and the amount of last meal calories had no significant affect to the false positive GCT (p = 0.64). The blood collection time distribution is shown in Fig. 3. The only associated factor with the false positive GCT, which had a p value of less than 0.2, was the period of test (morning or afternoon). The multivariable analysis was done and there was no significant effect with the false positive GCT rate when it was adjusted with the time since last meal (Table 3).

Table 3. Comparison of false-positive result of 50 grams GCT between various time since last meal and calories of meal.

Group and type of meal	Total GCT (n)	False positive GCT (%)	Risk ratio (95%CI)	Adjusted risk ratio (95%CI)	p value
Time since last meal					
< 1 hour	114	41 (36.0%)	1.72 (1.42-2.86)	1.60 (1.14-2.24)[a]	0.006
≥ 1 hour	312	65 (20.8%)			
< 2 hours	245	73 (29.8%)	1.63 (1.13-2.35)	1.53 (1.06-2.22)[a]	0.023
≥ 2 hours	181	33 (18.2%)			
< 3 hours	357	92 (25.8%)	1.27 (0.77-2.09)	1.23 (0.75-2.04)[a]	0.397
≥ 3 hours	69	14 (20.3%)			
Calories of last meal					
Mean ± SD	389.8 ± 188.6	380.3 ± 188.9	1.00 (0.99-1.00)	NA	0.546
Light meal	150	37 (24.7%)	1.01 (0.71-1.43)	NA	0.939
Heavy meal	276	69 (25%)			
Light meal within 2 hours	80	24 (30%)	0.98 (0.66-1.49)	NA	0.961
Heavy meal within 2 hours	165	49 (29.7%)			
Time of GCT (blood collecting time)					
8.00 am to 12.00 pm	296	64 (21.6%)	1.49 (1.07-2.07)	1.36 (0.98-1.91)[b]	0.07
12.01 pm to 16.00 pm	130	42 (32.3%)			

[a] adjusted with time of GCT

[b] adjusted with time since last meal ≥ 2 hours

GCT: glucose challenge test, CI: confidence interval, SD: standard deviation

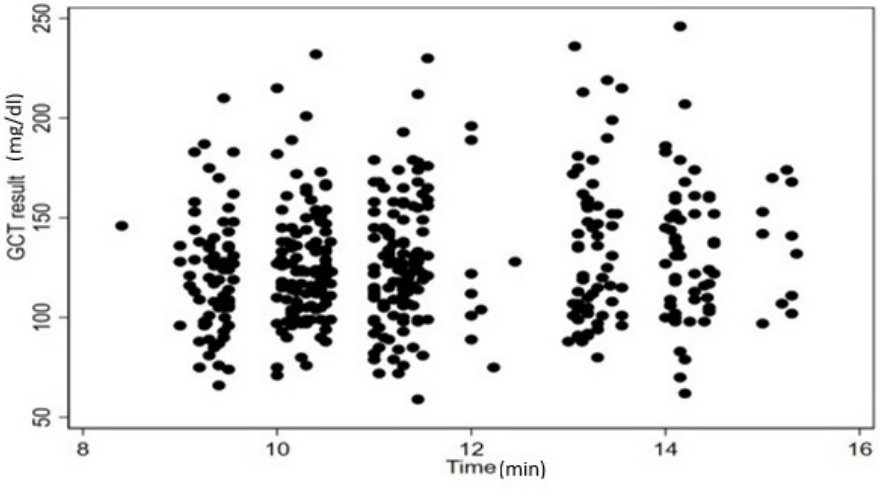

Fig. 3. Distribution between time of blood collection and result of 50 grams glucose challenge test (mg/dl).

Discussion

Gestational diabetes is the most common endocrine problem in pregnancy which has an impact as to pregnancy outcomes. There is still not a satisfactory detection method for this disease[1-10]. At present, there is no consensus regarding diagnostic tools between the one and two step methods, although the one step approch has greater proportion of women diagnosed with GDM but outcome of feto-maternal complications such as fetal macrosomia, cesarean section rate, birth trauma, etc. still no significant in both one and two step diagnostic methods[9-12]. A two-step approach method was applied in various countries for GDM diagnosis with different cut-off times for the 3 hour OGTT by NDDG and Carpenter and Coustan. The Carpenter and Coustan threshold could include a greater amount of pregnant women with GDM implied to a greater detection of feto-maternal complications[32, 33] but absence of clear comparative trials. Due to unclear benefit between Carpenter and NDDG cut-off, so our hospital decided to use NDDG cut-off in clinical practice. The two steps approach method could be applied to non-fasting pregnant woman that is more facilitative to use in various countries including Thailand[1, 34].

This study showed: first, GDM prevalence was 5.8% which was compatible with the previous studies which reported prevalence between 1.5-9.3%[3-7]. Second, false positive GCT prevalence was 24.9% which was similar to a previous report of between 8.8%-37.4%[19, 20, 35]. The prevalence increased if the Carpenter's criteria was used for diagnosis. The wide range for GDM prevalence and false positive GCT prevalence from previous studies were also due to the different diagnostic methods and GCT cut-off points, GDM detection and diagnosis[9, 10, 34, 36, 37].

The results from this study found that the time since last meal had an impact on the blood glucose level after a 50g GCT and a false positive GCT test (positive GCT but negative 100 g OGTT) especially when a last meal within 1 hour and 2 hours with RR 1.72 (1.42-2.86) and 1.63 (1.13-2.35), respectively. The results were comparable with previous studies by Sermer et al[25] and Cetin et al[26] who had reported the impact of time since last meal had an effect on mean plasma glucose. These former prior studies suggested the new cut-off level of 50 grams GCT if the time since last meal was < 2 hours in order to increase the results positive predictive value and specificity.

There were some previous studies about the effects of the period of the day, especially in the afternoon and at night, could decrease blood glucose GCT due to maternal metabolism and β-cell function[27, 28]. In contrast, Wong et al[37] and McElduff et al[38] reported that the afternoon GCT had higher positive rate but lower rate of GDM diagnosis due to cortisol metabolism. Data from this study found that the afternoon GCT (12.00 pm -16.00 pm) after the adjusted effect of time since last meal had no effect on the false positive GCT result. The calories of meal in this study had also less effect to glucose level of GCT which was compatible with a study that found a diet with low, medium, or high glycemic index had no effect on the GCT result[39].

The strength of this study were: first, a prospective observational cohort study which had the strength of potential relationship between exposure and outcome. Second, although the step approach to GDM diagnosis is one of the methods widely used, there are few studies about the factors for false positive in this test. This study found the factor of food and time since last meal to affect the false positive GCT result. Third, from the previous studies review this topic was the first study, which focused on the time and type of meal to false positive effect of GCT and last, the result of this study is easy to advice and apply for practical use.

There had some limitations with this study: first, recall bias, because even this study was a prospective cohort study, the information from participants about the previous meal and time intake might not be precise information. Second, the definition of light and heavy meals was applied from other countries (due to a lack of a Thai classification), thus the difference in food type might have some misclassification. Third, the risk approach screening GCT was used in this study because it is the routine practice of our center and many other centers in Thailand. A higher rate of GDM is assumed if routine GCT screening is performed.

Finally, there were lack of information of the effect of false positive GCT to the pregnancy outcome in this study. The long-term study is needed to access this effect.

Conclusion

Time since last meal had an impact to the false positive GCT result. A Time interval of more than 2 hours before the 50 grams GCT is suggested to avoid the unnecessary investigation for GDM screening.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. American College of Obstetricians and Gynecologists. Committee on Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018;131:e49-e64.
2. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al. Williams Obstetrics. 25th ed. McGraw-Hill education, New York 2018:1097-1114.
3. Serirat S, Deerochanawong C, Sunthornthepvarakul T, Jinayon P. Gestational diabetes mellitus. Thai J Obstet Gynaecol 1992;75:315-9.
4. Boriboonhirunsarn D, Sunsaneevithayakul P, Nuchangrid M. Incidence of gestational diabetes mellitus diagnosed before 20 weeks of gestation. Thai J Obstet Gynaecol 2004;87:1017-21.
5. Chanprapaph P, Sutjarit C. Prevalence of gestational diabetes mellitus (GDM) in women screened by glucose challenge test (GCT) at Maharaj Nakorn Chiang Mai Hospital. J Med Assoc Thai 2004;87:1141-6.
6. Sunsaneevithayakul P, Boriboohirunsarn D, Sutanthavibul A, Ruangvutilert P, Kanokpongsakdi S, Singkiratana D, et al. Risk factor-based selective screening program for gestational diabetes mellitus in Siriraj Hospital: result from clinical practice guideline. Thai J Obstet Gynaecol 2003;86:708-14.
7. Arora D, Arora R, Sangthong S, Leelaporn W, Sangratanathongchai J. Universal screening of gestational diabetes mellitus: prevalence and diagnostic value of clinical risk factors. J Med Assoc Thai 2013;96:266-71.
8. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. Prev Chronic Dis 2014;11:E104.
9. Saccone G, Khalifeh A, Al-Kouatly HB, Sendek K, Berghella V. Screening for gestational diabetes mellitus: one step versus two step approach. A meta-analysis of randomized trials. J Matern Fetal Neonatal Med 2020;33:1616-24.
10. Li-zhen L, Yun X, Xiao-Dong Z, Shu-bin H, Zi-lian W, Adrian Sandra D, et al. Evaluation of guidelines on the screening and diagnosis of gestational diabetes mellitus: systematic review. BMJ Open 2019;9:e023014.
11. Farrar D, Duley L, Dowswell T, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev 2017;8:Cd007122.
12. Palatnik A, Swanson K, Churchill T, Bilski A, Grobman WA, Miller ES. Association between type of screening for gestational diabetes mellitus and cesarean delivery. Thai J Obstet Gynaecol 2017;130:539.
13. Grotegut CA, Tatineni H, Dandolu V, Whiteman VE, Katari S, Geifman-Holtzman O. Obstetric outcomes with a false-positive one-hour glucose challenge test by the Carpenter-Coustan criteria. J Matern Fetal Neonatal Med 2008;21:315-20.
14. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 2002;25:1862-8.
15. England LJ, Dietz PM, Njoroge T, Callaghan WM, Bruce C, Buus RM, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. Am J Obstet Gynecol 2009;200:365.e1-.e8.
16. Sivaraman SC, Vinnamala S, Jenkins D. Gestational diabetes and future risk of diabetes. J Clin Med Res 2013;5:92.
17. Figueroa D, Landon MB, Mele L, Spong CY, Ramin SM, Casey B, et al. Relationship between 1-hour glucose challenge test results and perinatal outcomes. Obstet Gynecol 2013;121:1241-7.
18. Kemal Akpak Y, Gün I, Kaya N, Atay V. A comparison of pregnant subgroups with positive 50-gram glucose challenge test results to those with negative results in terms of obstetric and perinatal outcomes. Med Glas (Zenica) 2012;9:262-7.
19. Stamilio DM, Olsen T, Ratcliffe S, Sehdev HM, Macones GA. False-positive 1-hour glucose challenge test and adverse perinatal outcomes. Obstet Gynecol

2004;103:148-56.
20. Thananyai A, Panchalee T, Borriboonhiransan D. Prevalence of false positive 50-g glucose challenge test in risk-based ccreening before 20 weeks of gestation and relationship with adverse pregnancy outcomes. Thai J Obstet Gynaecol 2020;28:34-43.
21. Moebus S, Göres L, Lösch C, Jöckel K-H. Impact of time since last caloric intake on blood glucose levels. Eur J Epidemiol 2011;26:719-28.
22. Poirier P, Tremblay A, Catellier C, Tancrède G, Garneau C, Nadeau A. Impact of time interval from the last meal on glucose response to exercise in subjects with type 2 diabetes. J Clin Endocrinol Metab 2000;85:2860-4.
23. Reynolds AN, Venn BJ. The timing of activity after eating affects the glycaemic response of healthy adults: A randomised controlled trial. Nutrients 2018;10:1743.
24. Meng H, Matthan NR, Ausman LM, Lichtenstein AH. Effect of prior meal macronutrient composition on postprandial glycemic responses and glycemic index and glycemic load value determinations. Am J Clin Nutr 2017;106:1246-56.
25. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie J, Farine D, et al. Impact of time since last meal on the gestational glucose challenge test: the Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1994;171:607-16.
26. Cetin M, Cetin A. Time-dependent gestational diabetes screening values. Int J Gynaecol Obstet 1997;56:257-61.
27. Goldberg RJ, Ye C, Sermer M, Connelly PW, Hanley AJ, Zinman B, et al. Circadian variation in the response to the glucose challenge test in pregnancy: implications for screening for gestational diabetes mellitus. Diabetes Care 2012;35:1578-84.
28. Wang P, Lu M-C, Yu C-W, Yan Y-H. Influence of the time of day and fasting duration on glucose level following a 1-hour, 50-gram glucose challenge test in pregnant women. PloS one 2014;9:e112526.
29. The Royal Thai College of Obstetricians and Gynaecologists. Diabetes mellitus screening in pregnancy. In: Clinical Practice Guidelines. RTCOG 2017;1.170-84.
30. Medical complications in elderly gravida. Srinagarind Med J 2007;22:39-42.
31. Kimberley E. How many calories are in a low calorie meal? In: The spruce eats; 2019.
32. Ferrara A, Hedderson MM, Quesenberry CP, Selby JV. Prevalence of gestational diabetes mellitus detected by the national diabetes data group or the carpenter and coustan plasma glucose thresholds. Diabetes Care 2002;25:1625-30.
33. Cheng YW, Block-Kurbisch I, Caughey AB. Carpenter-Coustan criteria compared with the national diabetes data group thresholds for gestational diabetes mellitus. Obstet Gynecol 2009;114:326-32.
34. Behboudi-Gandevani S, Amiri M, Yarandi RB, Tehrani FR. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetol Metab Syndr 2019;11:11.
35. Gumus II, Turhan NO. Are patients with positive screening but negative diagnostic test for gestational diabetes under risk for adverse pregnancy outcome? J Obstet Gynaecol Res 2008;34:359-63.
36. Lu M-C, Huang S-S, Yan Y-H, Wang P. Use of the National Diabetes Data Group and the Carpenter-Coustan criteria for assessing gestational diabetes mellitus and risk of adverse pregnancy outcome. BMC Pregnancy Childbirth 2016;16:231.
37. Wong VW, Garden F, Jalaludin B. Hyperglycaemia following glucose challenge test during pregnancy: When can a screening test become diagnostic? Diabetes Res Clin Pract 2009;83:394-6.
38. McElduff A, Hitchman R. Screening for gestational diabetes: the time of day is important. Med J Aust 2002;176:136.
39. Southgate KM. The effect of a low glycemic index diet on glucose challenge test results in women at risk for gestational diabetes mellitus. University of Toronto 2012:1-124.

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OBSTETRICS

Medical Abortion at Gestational Age ≤ 24 weeks at Songklanagarind Hospital

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ABSTRACT

Objectives: To determine the success and complication rates of medical abortion at gestational age ≤ 24 weeks, and to identify their associated factors.

Materials and Methods: A retrospective study was conducted from January 2006 to December 2017. Medical records of pregnant women at gestational age ≤ 24 weeks, who were admitted for medical abortion, were reviewed. Spontaneous abortion was excluded. Multivariate logistic regression analysis was used to identify factors associated with success and complications. A p value of < 0.05 was considered statistically significant.

Results: A total of 717 cases were reviewed. Two medical regimens were used, including misoprostol alone (84.7%) and mifepristone-misoprostol (MM) (15.3%). The overall success rates in the first and second trimester were 65.8% and 79.3%. The highest success rate was observed in women at gestational age of ≤ 9 weeks, with the MM regimen (92.0%). The overall complication rate was 5.3%, including hemorrhage requiring blood transfusion (4.7%) and infection (0.6%). The complication rates in the first and second trimester were 2.5% and 5.6%, respectively. One factor associated with success in the first trimester was the drug regimen (MM); while that in the second trimester was maternal age. Multivariate analysis showed that factors associated with complications in the second trimester were multigravida and having an underlying disease.

Conclusion: Medical abortion at gestational age ≤ 24 weeks had low complications. Multigravida and having an underlying disease were factors associated with complications in the second trimester.

Keywords: medical abortion, mifepristone, misoprostol, complication.

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การยุติการตั้งครรภ์โดยการใช้ยาที่อายุครรภ์ไม่เกิน 24 สัปดาห์ ณ โรงพยาบาลสงขลานครินทร์

วรรณพร สุดสาย, จิตเกษม สุวรรณรัฐ, ธนพันธ์ ชูบุญ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราความสำเร็จ ภาวะแทรกซ้อน และปัจจัยที่มีผลต่อความสำเร็จและภาวะแทรกซ้อน ของการยุติการตั้งครรภ์โดยการใช้ยาที่อายุครรภ์ไม่เกิน 24 สัปดาห์*

วัสดุและวิธีการ: *เป็นการศึกษาวิจัยแบบย้อนหลัง โดยเก็บข้อมูลจากเวชระเบียนของสตรีที่ตั้งครรภ์ไม่เกิน 24 สัปดาห์ที่นอนโรงพยาบาลเพื่อใช้ยายุติการตั้งครรภ์ โดยไม่รวมสตรีตั้งครรภ์ที่มีภาวะแท้งบุตรเองตามธรรมชาติตั้งแต่เดือนมกราคม พ.ศ.2549 ถึงธันวาคม พ.ศ.2560 วิเคราะห์ข้อมูลโดยใช้สถิติเชิงพรรณนาและการวิเคราะห์การถดถอยพหุแบบโลจิสติกส์เพื่อหาปัจจัยที่มีผลต่อความสำเร็จและภาวะแทรกซ้อนจากการใช้ยาในการยุติการตั้งครรภ์ โดยกำหนดค่า p value < 0.05 ถือว่ามีนัยสำคัญทางสถิติ*

ผลการศึกษา: *ผู้ป่วยทั้งหมด 717 ราย ได้รับการยุติการตั้งครรภ์โดยใช้ยา 2 สูตรได้แก่ misoprostol อย่างเดียว (ร้อยละ 84.7) และ mifepristone ร่วมกับ misoprostol (MM) (ร้อยละ 15.3) อัตราความสำเร็จรวมของยาทั้ง 2 สูตรในไตรมาสแรกและไตรมาสที่สองคือร้อยละ 65.8 และร้อยละ 79.3 ตามลำดับ อัตราความสำเร็จพบมากที่สุดในผู้ป่วยที่ใช้ยาสูตร MM ที่มีอายุครรภ์ไม่เกิน 9 สัปดาห์ (ร้อยละ 92) ภาวะแทรกซ้อนโดยรวมคิดเป็นร้อยละ 5.3 ได้แก่ ตกเลือดและต้องได้รับส่วนประกอบของเลือด (ร้อยละ 4.7) และติดเชื้อ (ร้อยละ 0.6) ภาวะแทรกซ้อนในไตรมาสแรกและไตรมาสที่สองพบร้อยละ 2.5 และร้อยละ 5.6 ตามลำดับ ปัจจัยที่มีผลต่อความสำเร็จในไตรมาสแรกได้แก่สูตรยาที่ใช้ ส่วนในไตรมาสที่สองได้แก่อายุ ส่วนปัจจัยที่มีผลต่อภาวะแทรกซ้อนในไตรมาสที่สองได้แก่ การตั้งครรภ์หลังและการมีโรคประจำตัว*

สรุป: *การใช้ยายุติการตั้งครรภ์ที่อายุครรภ์ไม่เกิน 24 สัปดาห์ มีภาวะแทรกซ้อนต่ำ การตั้งครรภ์หลัง และการมีโรคประจำตัว เป็นปัจจัยที่สัมพันธ์กับการเกิดภาวะแทรกซ้อนในไตรมาสที่สอง*

คำสำคัญ: *การใช้ยาในการยุติการตั้งครรภ์, mifepristone, misoprostol, ภาวะแทรกซ้อน*

Introduction

Since 1960, surgical abortion has been a method of choice for early pregnancy termination. Until 1970, medical abortion had become an alternative method with the use of prostaglandins, and then with anti-progesterone in 1980[1]. Medical abortion is an effective, acceptable and safe method. It can be used in early pregnancy, up to 24 weeks of gestation[2, 3]. The most effective medical abortion regimen is a combination of mifepristone and misoprostol[1, 4], as this has higher efficacy, shorter duration of abortion and lower complications than the use of misoprostol alone[4, 5]. However, high variation in doses, timing and route of administration still exists. The World Health Organization (WHO) recommends a 200 mg of mifepristone, followed by 800 mcg of misoprostol in pregnancies up to 63 days of gestation[6]. This regimen is highly effective, with low failure rates (2%-5%)[1,7]. Recent studies have demonstrated acceptable efficacy and low complications in more advanced gestational ages with higher efficacy for repeated dosages of misoprostol[8].

Our institution, Songklanagarind Hospital, a university hospital in Southern Thailand, has provided safe abortions for women with maternal and fetal indications for a long period. The database from the Medical Statistics Unit, Department of Obstetrics and Gynecology, Songklanagarind Hospital has shown an increasing trend of medical abortion during the past ten years: from 30 cases to 130 cases per year. Situation analysis of medical abortion in our hospital has never been studied. Therefore, we conducted this research to determine the success and complication rates of medical induced abortion at gestational age ≤ 24 weeks, and to identify their associated factors. These results can be used for improvement of quality of abortion care, and close surveillance in women at risk for serious complications.

Materials and Methods

The retrospective descriptive study was conducted after approval by the Institutional Review Board of Faculty of Medicine, Prince of Songkla University (REC.62-262-12-4).

Medical records of women who were admitted for induced abortion at Songklanagarind Hospital, from January 2006 to December 2017 were reviewed. Data were retrieved from the database of the Medical Statistics Unit, Department of Obstetrics and Gynecology, and the Hospital Information System of Songklanagarind Hospital. The inclusion criteria were 1) gestational age ≤ 24 weeks, and 2) admitted for medical abortion. The exclusion criteria were 1) spontaneous abortion, 2) medical use for cervical preparation before surgical procedure, and 3) surgical abortion.

Maternal age, gestational age at termination, gravidity, underlying diseases, history of previous uterine surgery and curettage, indications for termination of pregnancy, drug regimens for termination of pregnancy, status of abortion (success or failure), complications, requirement of blood transfusion and duration of hospital stay were collected.

The primary outcome was complication rate of medical abortion at gestational age ≤ 24 weeks. The secondary outcomes were success rate and factors associated with complications and success of medical abortion.

Success of medical abortion was defined as complete expulsion without additional treatment[9] within 72 hours. Failure of medical abortion was defined as ongoing pregnancy, need for additional treatment or no abortion after five doses of misoprostol[9]. Complications included major adverse outcomes, such as hemorrhage requiring blood transfusion, infection (related to abortion, such as endometritis or metritis) and uterine rupture[10]. Duration of termination was defined as time from first dose of misoprostol to expulsion of conceptus or fetus[11]. First trimester was defined as gestational age < 13 weeks[12]. Early first trimester was defined as gestational age ≤ 63 days[5, 6]. Late first trimester was defined as gestational age 64-90 days. Second trimester was defined as gestational age 13-24 weeks[12].

Sample size was calculated using a formula for a prevalence study; with $p = 0.067$[10] (the prevalence of complications associated with medical abortion),

alpha = 0.05 and d = 0.02; a total of 601 cases being required. We added 15% more cases for missing data, so at least 692 eligible cases were recruited.

Descriptive statistics and multivariate logistic regression were used for data analysis. A p value of < 0.05 was considered statistically significant.

Results

During a 12-year period, there were 1,227 cases admitted for termination of pregnancy. We excluded 510 cases who did not meet the criteria, including: gestational age > 24 weeks, spontaneous abortion, medical use for cervical preparation before surgical procedure and admitted for surgical abortion.

Finally, a total of 717 cases were studied. There were two regimens used: misoprostol alone (84.7%) and a combination of mifepristone-misoprostol (15.3%). Regarding route of administration of misoprostol: vaginal route was the most common (77.4%) with the remaining being sublingual (22.6%). The regimens and routes were selected by an obstetrician in-charge.

The MM regimen consists of 200 mg of mifepristone and 800 mcg of misoprostol, provided by the Department of Health, Ministry of Public Health, Thailand. It is free of charge. Mifepristone was taken first and followed by misoprostol within the next 24-48 hours. This regimen was used for gestational ages of up to 63 days.

In the second trimester, the MM regimen was administered, followed by repeated doses of misoprostol until expulsion. Between 2006 and 2014, there was only misoprostol alone regimen in use, with MM regimen becoming available in 2015. Dosage of misoprostol use (200 mcg or 400 mcg every 3, 6, 8, 12 or 24 hours) depended on the preference of the obstetrician in-charge, with a maximum of five doses.

Demographic and obstetric data are shown in Table 1. About two-thirds of cases were below 35 years of age. Most women were in their second trimester. Approximately one-third of cases had underlying diseases, which were: hypertension (5.9%), heart diseases (4.9%), psychiatric disease (3.2%), systemic lupus erythematosus (2.4%), diabetes mellitus (1.4%) and hyperthyroidism (1.3%).

Table 1. Demographic characteristics and obstetric data (n = 717).

	Median (IQR)	n	Percent
Age (years)	31 (24, 37)		
< 35		458	63.9
≥ 35		259	36.1
Religion			
- Buddhism		598	83.4
- Islam		116	16.2
- Christianity		3	0.4
Primigravida		344	48.0
GA ≥ 13 weeks		638	89.0
Underlying diseases		201	28.0
Hospital stay (days)	2 (2, 3)		

IQR: interquartile range

The indications for pregnancy termination are shown in Table 2, and they show higher rates of fetal indication than that of maternal. Three-fourths of cases with fetal indications were due to abnormal chromosomes or congenital anomalies. For maternal indications, socioeconomic problems were the leading cause, followed by medical diseases and sexual assaults.

Table 2. Indication for induced abortion (n = 717).

Indication	n	percent
Maternal indications	290	40.5
Medical diseases	71	9.9
Psychiatric disorder	19	2.6
Teratogen exposure	7	1.0
Socioeconomic problems	161	22.5
Sexual assault	32	4.5
Fetal indications	427	59.5
Dead fetus in utero	111	15.5
Abnormal chromosomes	155	21.6
Fetal anomalies	161	22.4

Of the 717 cases, 79 were in the first trimester and 638 were in the second trimester. Table 3 shows drug regimens used for pregnancy termination, success rates and duration of termination. With regard to first trimester abortions, approximately 60% of cases were in the late first trimester. The highest success rate was noted in the MM regimen at gestational age ≤ 63 days.

Table 3. Drug regimens for medical abortion, success rates and duration of termination.

Drug regimen	n	percent	Success rate (%)	Duration of termination (hours) median (IQR)
First trimester	79	100	65.8	
Gestational age ≤ 63 days	33	41.8	75.8	
Mifepristone-misoprostol	25	75.8	92.0	4.0 (2.7,6.1)
Misoprostol	8	24.2	25.0	15.5 (6.0,23.3)
Gestational age 64 - 90 days	46	58.2	58.7	
Mifepristone-misoprostol	23	50.0	73.9	4.5 (3.2,6.8)
Misoprostol	23	50.0	43.5	10.3 (5.5,15.7)
Second trimester	638	100	79.3	
Mifepristone-misoprostol	62	9.7	82.3	6.2 (4.1,8.6)
Misoprostol alone	576	90.3	79.0	15.4 (10.0,29.0)
- Misoprostol 200 mcg every 3 hours	4	0.7	50.0	
- Misoprostol 400 mcg every 3 hours	54	9.4	79.6	12.2 (8.3,18.3)
- Misoprostol 400 mcg every 6 hours	151	26.2	83.4	15.4 (9.6,30.0)
- Misoprostol 400 mcg every 8 hours	100	17.4	71.0	18 (11.0,30.4)
- Misoprostol 400 mcg every 12 hours	183	31.8	82.0	16.4 (11.5,29.0)
- Misoprostol 400 mcg every 24 hours	3	0.5	66.7	
Others	81	14.1	75.3	

IQR: interquartile range

Focusing on 576 cases in the second trimester terminated by the misoprostol alone regimen, there was wide variations of dosage and intervals of misoprostol administration, depending on the obstetricians' preference. A dosage of 400 mcg every 12 hours was the most commonly used regimen, followed by 400 mcg every 6 hours and 400 mcg every 8 hours, respectively, with success rates of approximately 70-80%. (Table 3). Dosage of 400 mcg every 3 hours had the shortest duration of termination.

Regarding 27 failure cases in the first trimester: 20 cases (all in late first trimester) received second cycle of misoprostol alone with success, five cases ended up with manual vacuum aspiration and two cases had spontaneous abortion within few days. With regard to 132 failure cases in the second trimester, 118 cases underwent surgical evacuation, nine cases received second cycle of misoprostol alone regimen with success, four cases had spontaneous abortion and one case ended up with hysterotomy.

To identify factors associated with success of medical abortion in the first trimester, univariate analysis was performed and showed that only drug regimen (MM) was significant. However, in the second trimester, there were two significant factors: maternal age (< 35 years) and gravidity (primigravida) (Table 4). Multivariate analysis showed that only maternal age (< 35 years) was significant in the second trimester (adjusted odds ratio 1.78, 95% confidence interval 1.23-2.59, p = 0.002), adjusted by gravidity.

Regarding complications of abortion, there were only two cases (2/79, 2.5%) in the first trimester and 36 cases (36/638, 5.6%) in the second trimester. The overall complication rate was 5.3%, including hemorrhage requiring blood transfusion (4.7%), and infection (0.6%). No maternal death or uterine rupture was reported in this study. Since there were only 2 cases with complications in the first trimester, multivariate analysis could not be performed.

Table 4. Univariate analysis of factors associated with success of medical abortion.

Factor	First trimester (n = 79)			Second trimester (n = 638)		
	n	Percent of success	p value	n	Percent of success	p value
Age (years)			0.954			< 0.001
< 35	53	66.0		405	84.0	
≥ 35	26	65.4		233	71.2	
Gravidity			0.509			0.029
Primigravida	34	61.8		310	82.9	
Multigravida	45	68.9		328	75.9	
Regimen			< 0.001			0.546
Mifepristone-misoprostol regimen	47	81.6		62	82.3	
Misoprostol alone	30	40.0		576	79.0	
Underlying diseases			0.296			0.404
Yes	61	55.6		173	81.5	
No	18	68.9		465	78.5	
Indication for induced abortion			0.206			0.573
Maternal indication	62	69.4		226	80.5	
Fetal indication	17	52.9		412	78.6	

To identify factors associated with complications in the second trimester, a univariate analysis was performed. It was found that four variables including maternal age, gravidity, a history of uterine curettage and having an underlying disease, were significant (Table 5). A history of uterine surgery and drug regimen were not statistically significant. Multivariate logistic regression analysis was performed with six variables in the final model: maternal age (< 35 vs > 35 years), gravidity (primigravida vs multigravida), a history of uterine curettage (yes/no), a history of uterine surgery (yes/no), drug regimen (MM vs misoprostol alone) and having underlying diseases (yes/no). The only two significantly associated factors were gravidity and having an underlying disease (Table 5).

Table 5. Multivariate logistic regression analysis of factors associated with complications in the second trimester (n = 638).

Variables	Crude odds ratio (95% confidence interval)	p value	Adjusted odds ratio (95% confidence interval)	p value
Maternal age ≥ 35 years	2.0 (1.0-4.0)	0.040	1.5 (0.7-3.0)	0.300
Multigravida	3.0 (1.4-6.5)	0.005	2.4 (1.0-5.5)	0.046
Underlying disease	2.3 (1.2-4.5)	0.019	2.1 (1.1-4.2)	0.037
History of uterine surgery	2.0 (0.9-4.1)	0.073	1.2 (0.5-2.7)	0.680
History of uterine curettage	2.8 (1.2-6.4)	0.016	2.3 (0.9-5.4)	0.065
Medical regimens (misoprostol alone)	1.9 (0.4-8.0)	0.393	1.8 (0.4-8.0)	0.426

Discussion

Medical abortion at gestational age ≤ 24 weeks was effective and safe. Low complication rate was noted. Factors associated with complications in the second trimester were multigravida and having an underlying disease. Factors associated with success in the first trimester was the drug regimen (MM), whilst in the second trimester, it was maternal age (< 35 years).

In our study, the success rate of the MM regimen at gestational age ≤ 63 days (92%) was comparable to previous studies, ranging from 92-99.6%[13-16]. With regard to late first trimester abortions, the overall success rate of this study (58.7%) was lower than previous reports (78.6%-94.6%)[13]. This could be explained by 1) we declared failure of medical abortion quite early, and urgently proceeded to manual vacuum aspiration to ensure complete abortion, and 2) repeated doses of misoprostol were rarely administered in the MM regimen, especially in the early period of drug implementation. However, we had a very low success rate for the misoprostol alone regimen due to unavailable protocols for drug use, especially before 2012. In addition, we had only a few cases terminated by misoprostol alone. We preferred manual vacuum aspiration for early pregnancy termination to medical abortion, especially before 2015, when the MM regimen was not available. The MM regimen had higher success rates and shorter duration of termination than misoprostol alone, similar to previous studies[1].

Regarding second trimester abortions, the overall success rate (79%) was quite low, compared to previous studies (82-92%)[11,17]. It could be explained by that we did not have a protocol for medical abortion. Wide variations of dosage of misoprostol were used depending on obstetrician in-charge. Median duration of termination for MM regimen in our study (6.2 hours) was comparable to previous studies (5.9-6.6 hours)[11]. International Federation of Gynecology and Obstetrics (FIGO) (2017) recommends the regimen of misoprostol 400 mcg every 3 hours[12]. However, we had only 10%

of cases using the FIGO (2017) regimen. We were afraid of uterine rupture, so most obstetricians preferred longer intervals of misoprostol administration. Even though we had longer intervals of misoprostol administration than that recommended by FIGO, all prescribed regimens had a median duration of termination of 15.6 hours (12-18 hours), comparable to previous studies (10-15 hours)[18-21]. We found the longer intervals of misoprostol administration, the longer the duration of termination. We capped the number of misoprostol doses to a maximum of five. However, recent studies recommended continuous dosing of misoprostol until expulsion rather than capping the number of doses[8].

Drug regimen was the only factor associated with success in the first trimester. This is not surprising, because the mechanism of action of the MM regimen was better than that of misoprostol alone. The mifepristone blocked the progesterone receptor, leading to a change in the endometrial lining and detachment of the decidua, softening and dilation of the cervix and increased uterine sensitivity to prostaglandin. In addition, misoprostol acted by softening the cervix and uterine contractility, resulting in the expulsion of the product of conception[22]. However, in the second trimester, only maternal age (< 35 years) was a significant factor of success. This was similar to previous study[23].

Multigravida and having an underlying disease were significant factors associated with complications in the second trimester. For multigravida, increased complications were also found in previous study[24]. Since common complications in our study were hemorrhage and infection, therefore, it might be related to other factors which were higher rates in multigravida, such as coexisting genital tract infection, advanced maternal age, history of uterine scar and history of uterine curettage. Women with underlying diseases, such as heart disease, hypertension, autoimmune disease and diabetes mellitus, were at risk for hemorrhage and/or infection due to low immunity and/or receiving anti-coagulant.

The strengths of this study were: 1) an adequate sample size, 2) reliable and complete data, and 3) determination of factors associated with success and complications. The limitations of the study were: 1) it was a retrospective design, 2) no protocol of medical abortion management was available, and 3) declaration of failure depended on the judgement of obstetrician in-charge.

Conclusion

In conclusion, medical abortion at gestational age ≤ 24 weeks was safe. Obstetricians should pay special attention to multigravida women, and those having an underling disease for close surveillance, so as for early detection of serious complications.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev 2011;(11):CD002855.
2. Baiju N, Acharya G, D'Antonio F, Berg RC. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG 2019;126:1536-44.
3. Tang OS, Ho PC. Medical abortion in the second trimester. Best Pract Res Clin Obstet Gynaecol 2002;16:237-46.
4. Shah D, Rijal P, Thakur A, Rai R. Mifepristone and misoprostol vs misoprostol alone in second trimester termination of pregnancy. J Nepal Med Assoc 2018;56:856-60.
5. Abubeker FA, Lavelanet A, Rodriguez MI, Kim C. Medical termination for pregnancy in early first trimester (≤ 63 days) using combination of mifepristone and misoprostol or misoprostol alone: a systematic review. BMC Womens Health 2020;20:142.
6. Meena SR. Comparative study of mifepristone with vaginal misoprostol for first trimester termination of pregnancy at different gestational ages. J Obstet Gynaecol India 2016;66:426-30.

7. Raymond EG, Trussell J, Polis CB. Cost-effectiveness of increased access to emergency contraceptive pills: probably not. Contraception 2013;87:504-8.
8. Lerma K, Shaw KA. Update on second trimester medical abortion. Curr Opin Obstet Gynecol 2017;29:413-8.
9. Fiala C, Cameron S, Bombas T, Parachini M, Agostini A, Lertxundi R, et al. Outcome of first trimester medical termination of pregnancy: definitions and management. Eur J Contracept Reprod Health Care 2018;23:451-7.
10. Carlsson I, Breding K, Larsson PG. Complications related to induced abortion: a combined retrospective and longitudinal follow-up study. BMC Womens Health 2018;18:158-66.
11. Heikinheimo O, Suhonen S, Haukkamaa M. One- and 2-day mifepristone-misoprostol intervals are both effective in medical termination of second-trimester pregnancy. Reprod Biomed Online 2004;8:236-9.
12. Morris JL, Winikoff B, Dabash R., Weeks A, Faundes A, Gemzell-Danielsson K, et al. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet 2017;138:363-6.
13. Kapp N, Eckersberger E, Lavelanet A, Rodriguez MI. Medical abortion in the late first trimester: a systematic review. Contraception 2019;99:77-86.
14. Dahiya K, Ahuja K, Dhingra A, Duhan N, Nanda S. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet 2012;285: 1055-8
15. Goldstone P, Walker C, Hawtin K. Efficacy and safety of mifepristone-buccal misoprostol for early medical abortion in an Australian clinical setting. Aust N Z J Obstet Gynaecol 2017;57:366-71.
16. Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.
17. Nissi R, Santala M, Immonen E, Talvensaari-Mattila A. Mifepristone and misoprostol is safe and effective method in the second-trimester pregnancy termination. Arch Gynecol Obstet 2016;294:1243-7.
18. Nigam A, Singh VK, Prakash A. Vaginal vs. oral misoprostol for mid-trimester abortion. Int J Gynaecol Obstet 2006;92:270-1.
19. Wong KS, Ngai CS, Wong AY, Tang LC, Ho PC. Vaginal misoprostol compared with vaginal gemeprost in termination of second trimester pregnancy. A randomized trial. Contraception 1998;58:207-10.
20. Wong KS, Ngai CS, Yeo EL, Tang LC, Ho PC. A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial. Hum Reprod 2000;15:709-12.
21. Pongsatha S, Tongsong T. Intravaginal misoprostol for pregnancy termination. Int J Gynaecol Obstet 2004;87:176-7.
22. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol 2009;2:159-68.
23. Haimov-Kochman R, Arbel R, Sciaky-Tamir Y, Brzezinski A, Laufer N, Yagel S. Risk factors for unsuccessful medical abortion with mifepristone and misoprostol. Acta Obstet Gynecol Scand 2007;86:462-6.
24. Bartley J, Tong S, Everington D, Baird DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost. Contraception 2000;62:297-303.

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GYNAECOLOGY

Risk Factors Associated with Parametrial Involvement in Early-stage Cervical Cancer

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ABSTRACT

Objectives: The study aimed to identify the risk factors affecting parametrial involvement in patients with early-stage cervical cancer.

Materials and Methods: The sample participated in the study was the patients with stage IA2 to IIA1 cervical cancer according to 2018 International Federation of Gynecology and Obstetrics (FIGO), who had been treated with radical hysterectomy and pelvic lymphadenectomy during April 2011 to April 2020. In term of methodology, the retrospective cross-sectional analysis was to determine the factors including tumor size, deep stromal invasion (DSI), lymphovascular space invasion (LVSI), pelvic node status, FIGO staging, age and histology (squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma), associated with parametrial involvement (PI).

Results: Overall, 19 of the 206 patients (9.22%) had PI. Patients with PI were more likely to have larger tumor size (> 4 cm: 15%, 2-4 cm: 10%, < 2 cm: 2%, $p = 0.02$), DSI (deep 1/3: 19%, middle 1/3: 2%, superficial 1/3: 0%, $p = 0.01$), LVSI (positive: 17%, negative: 3%, $p < 0.01$), metastasis to pelvic lymph nodes (positive: 50%, negative: 4%, $p < 0.01$), and higher FIGO stage (IB3: 16%, IB2: 10%, IB1: 3%, IA2: 0%, $p = 0.02$). Multivariate analysis showed that only deep stromal invasion ($p = 0.02$) and pelvic lymph node metastasis ($p < 0.01$) were independent risk factors for PI.

Conclusion: The deep stromal invasion and pelvic lymph node involvement were significantly associated with PI in multivariate analysis. Cervical cancer with superficial 1/3 stromal invasion and no pelvic lymph node metastasis seldom had PI.

Keywords: early-stage cervical cancer, parametrectomy, parametrial invasion.

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ปัจจัยเสี่ยงที่เกี่ยวข้องกับการลุกลามเข้าเนื้อเยื่อข้างปากมดลูกในโรคมะเร็งปากมดลูกระยะต้น

อธิวัฒน์ เตชะพะโลกุล, ยุทธนา ของทิพย์

บทคัดย่อ

วัตถุประสงค์: *เพื่อระบุปัจจัยเสี่ยงของการลุกลามของมะเร็งปากมดลูกเข้าสู่เนื้อเยื่อข้างปากมดลูก*

วัสดุและวิธีการ: *ศึกษาโดยสืบค้นข้อมูลของผู้ป่วยมะเร็งปากมดลูกระยะ IA2 ถึง IIA1 (International Federation of Gynecology and Obstetrics 2018 หรือ FIGO 2018) ที่ได้รับการผ่าตัดมดลูกแบบกว้างและผ่าตัดต่อมน้ำเหลืองอุ้งเชิงกรานตั้งแต่เดือนเมษายน พ.ศ. 2554 ถึง เดือนเมษายน พ.ศ. 2563 เป็นการศึกษาย้อนหลังแบบตัดขวางเพื่อระบุว่าขนาดของเนื้องอก ความลึกของการลุกลาม การกระจายของเซลล์มะเร็งไปในหลอดเลือดหรือน้ำเหลือง การกระจายไปที่ต่อมน้ำเหลืองอุ้งเชิงกราน ระยะโรค อายุ และจุลกายวิภาคศาสตร์เนื้อเยื่อ (squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma) มีปัจจัยใดที่มีความสัมพันธ์กับการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก*

ผลการศึกษา: *ผู้ป่วย 19 คน จาก 206 คน (ร้อยละ 9.22) พบมีการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก ผู้ป่วยที่มีการลุกลามเข้าเนื่อเยื่อข้างปากมดลูกมักจะมีขนาดของเนื้องอกใหญ่กว่า (> 4 เซนติเมตร: ร้อยละ 15, 2-4 เซนติเมตร: ร้อยละ 10, < 2 เซนติเมตร: ร้อยละ 2, p =0.02), ความลึกของการลุกลามมากกว่า (deep 1/3: ร้อยละ 19, middle 1/3: ร้อยละ 2, superficial 1/3: ร้อยละ 0, p = 0.01), พบการกระจายของเซลล์มะเร็งไปในหลอดเลือดหรือน้ำเหลืองบ่อยกว่า (positive: ร้อยละ 17, negative: ร้อยละ 3, p < 0.01), พบการกระจายไปที่ต่อมน้ำเหลืองอุ้งเชิงกรานบ่อยกว่า (positive: ร้อยละ 50, negative: ร้อยละ 4, p < 0.01) และระยะของโรค (FIGO stage) สูงกว่า (IB3: ร้อยละ 16, IB2: ร้อยละ 10, IB1: ร้อยละ 3, IA2: ร้อยละ 0, p = 0.02) การวิเคราะห์แบบหลายตัวแปรพบว่าความลึกของการลุกลาม (p = 0.02) และการลุกลามเข้าต่อมน้ำเหลืองอุ้งเชิงกราน (p < 0.01) เป็นปัจจัยเสี่ยงอิสระของการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก*

สรุป: *ความลึกของการลุกลาม และการลุกลามเข้าต่อมน้ำเหลืองอุ้งเชิงกรานมีความสัมพันธ์กับการลุกลามเข้าเนื้อเยื่อข้างปากมดลูกอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยโรคมะเร็งปากมดลูกที่มีความลึกของการลุกลามน้อยกว่า 1/3 ของความหนาเนื้อเยื่อปากมดลูกและไม่พบการกระจายไปที่ต่อมน้ำเหลืองอุ้งเชิงกรานแทบจะไม่พบการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก*

คำสำคัญ: *มะเร็งปากมดลูกระยะต้น, การตัดเนื้อเยื่อข้างปากมดลูก, การลุกลามเข้าเนื้อเยื่อข้างปากมดลูก*

Introduction

Cervical cancer is the fourth most common malignancy in females worldwide[1] and the second most common malignancy among Thai women[2]. The current standard surgical treatment of early-stage cervical cancer (stages IA2, IB, and IIA) is radical hysterectomy with pelvic lymphadenectomy[3].

Radical hysterectomy is associated with postoperative morbidity including lymphedema (3.6%), bladder atony (3.6%), bowel ileus (2.9%), sexual dysfunction (2.2%), ureterovaginal fistula (0.8%), and vesicovaginal fistula (0.4%). More importantly, it reduces the patient's quality of life[4]. Parametrectomy is the main cause of postoperative complication due to denervation of the autonomic nerve supply to the pelvic organs during the procedure[3]. At present, several studies aim to reduce this complication by omitting parametrectomy in patients who may benefit from less radical surgery without a negative impact on survival. Previous studies have shown that there are some pathologic factors associated with parametrial involvement (PI) and for some low-risk patients, resection of the parametrium may be spared[3, 5-7]. Patients with tumor size of < 2 cm in diameter, no deep stromal invasion (DSI), no lymphovascular space invasion (LVSI), and no lymph node involvement have been found to have less than 1% risk of PI. However, there have been inconsistent results among these studies and some of them have not been analyzed by multivariate analysis.

The main objective of this study was to identify the risk factors independently associated with PI in patients with early-stage cervical cancer.

Materials and Methods

This retrospective cross-sectional study reviewed medical records of all patients, diagnosed with stage IA2 to IIA1 cervical cancer, who had undergone radical hysterectomy and pelvic lymphadenectomy from April 2011 to April 2020. The study was approved by the Institutional Review Board of Chonburi Hospital.

Regarding the sample participated in the study; the patients whose radical hysterectomy were abandoned, had endometrial cancer, non-squamous cell, or non-adenocarcinoma cell type on the final pathology reports, or had inadequate medical record were excluded. The study started by obtaining the clinicopathological variables including age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, histology, DSI, LVSI, PI, and the status of pelvic lymph node. All the slides were reviewed by our pathologists at Chonburi Hospital. Additionally, the cancer staging was based on the criteria established by FIGO 2018[1]. Besides, histology was divided into squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma. With regard to tumor diameter which was obtained from the measurement of the hysterectomy specimen, we categorized into 3 groups: < 2 cm, 2-4 cm, and ≥ 4 cm according to tumor size cut-off of FIGO stage IB1, IB2 and IB3, respectively. In addition, the depth of invasion was categorized into 3 groups according to the proportion between the depth of the lesion and entire cervical thickness: superficial 1/3, middle 1/3, and deep 1/3 invasion. Also, PI was defined as a malignant cell in either parametrial tissue or parametrial lymph node.

SPSS for Windows, version 26.0. Chicago: SPSS Inc; 2019, was employed to discover statistical data. The sample size was calculated by using the Jacob Cohen's sample size calculating table[8]. It was met the medium population effect size with alpha error = 0.05 and 80% of the power in which the independent variables of 8 were equal to 107 patients. The baseline characteristic of the patients and the pathology results were described by the mean and standard deviation for continuous data, and number with percentage for nominal data. The associations between clinicopathologic factors and parametrial involvement were evaluated by binary logistic regression in both univariate and multivariate analysis. Probability values of < 0.05 were considered to be statistically significant.

Results

From April 2011 to April 2020, 294 patients underwent radical hysterectomy with pelvic lymphadenectomy. However, 88 patients were excluded from the analysis as shown in Fig. 1. The final study group comprised of 206 patients with a mean age of

47 ± 10.7 years. FIGO stage IA2, IB1, IB2, IB3, and IIA1 were found in 18 (8.74%), 38 (18.45%), 90 (43.69%), 58 (28.16%) and 2 patients (0.97%), respectively. Histopathology confirmed 131 (63.59%) squamous cell carcinomas, 55 (26.70%) adenocarcinomas, and 20 (9.71%) adenosquamous cell carcinomas. The clinicopathologic characteristics of the 206 patients are summarized in Table 1.

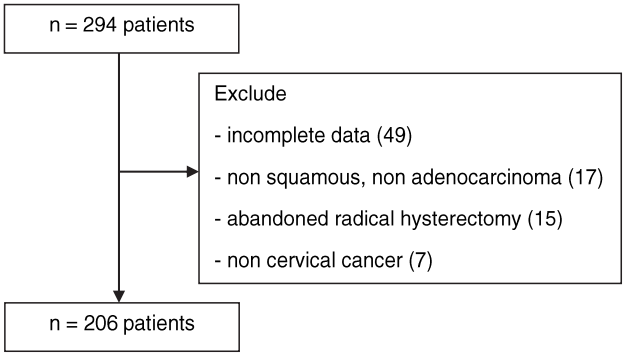

Fig. 1. Patient flow chart.

Table 1. Clinicopathologic characteristics of patients with cervical cancer who were treated with radical hysterectomy.

Characteristics	n
Age (years), mean ± SD	47 ± 10.7
Stage	
IA2	18 (8.7%)
IB1	38 (18.5%)
IB2	90 (43.6%)
IB3	58 (28.2%)
IIA1	2 (1.0%)
Histology	
Squamous cell carcinoma	131 (63.6%)
Adenocarcinoma	55 (26.7%)
Adenosquamous cell carcinoma	20 (9.7%)
Stromal invasion	
Superficial 1/3	64 (31.1%)
Middle 1/3	48 (23.3%)
Deep 1/3	94 (45.6%)
Tumor size	
< 2 cm	57 (27.7%)
2-4 cm	90 (43.7%)
≥ 4 cm	59 (28.6%)
Lymphovascular space invasion	
No	114 (55.3%)
Yes	92 (44.7%)
Parametrial involvement	
No	187 (90.8%)
Yes	19 (9.2%)
Pelvic lymph node involvement	
No	184 (89.3%)
Yes	22 (10.7%)

SD: standard deviation

Of the 206 patients, PI was found in 19 patients (9.22%). There was no PI found in any of the 18 patients with stage IA2. Twenty-two patients had pelvic lymph node metastasis and 50% of them had PI, while only 8 of the 184 patients (4.35%) with no pelvic lymph node involvement had PI. Table 2 demonstrates the univariate analysis of the potential risk factors for PI. Patients with PI were more likely to have higher disease stage (p = 0.02), larger tumor size (p = 0.01), deep stromal invasion (p = 0.02), presence of LVSI (p < 0.01), and pelvic node involvement (p < 0.01). However, when multivariate binary logistic regression was performed, only DSI (odds rartio (OR) 10.08; 95% confidence interval (CI) 1.35 - 75.14, p = 0.02) and pelvic lymph node involvement (OR 10.63; 95%CI 3.21 - 35.17, P < 0.01) were independently associated with PI (Table 3).

Table 2. Univariate analysis of potential risk factors for parametrial involvement.

Characteristics	PI, n (%)		OR (95%CI)	p value
	negative	positive		
Age (years), mean ± SD	47.13 ± 10.37	48.37 ± 14.21	1.01 (0.97-1.06)	0.63
Stage			2.10 (1.12-3.92)	0.02
IA2	18 (8.7%)	0 (0)		
IB1	38 (18.5%)	1 (3)		
IB2	90 (43.6%)	9 (10)		
IB3	58 (28.2%)	9 (16)		
IIA1	2 (1.0%)	0 (0)		
Histology			1.03 (0.51-2.08)	0.93
Squamous cell carcinoma	131 (63.6%)	12 (9)		
Adenocarcinoma	55 (26.7%)	5 (9)		
Adenosquamous cell carcinoma	20 (9.7%)	2 (10)		
Stromal invasion			13.49 (2.06-88.20)	0.01
Superficial 1/3	64 (31.1%)	0 (0)		
Middle 1/3	48 (23.3%)	1 (2)		
Deep 1/3	94 (45.6%)	18 (19)		
Tumor size			2.39 (1.18-4.83)	0.02
< 2 cm	56 (98)	1 (2)		
2 - 4 cm	81 (90)	9 (10)		
≥ 4 cm	50 (85)	9 (15)		
Lymphovascular space invasion			7.79 (2.19-27.66)	< 0.01
No	111 (97)	3 (3)		
Yes	76 (83)	16 (17)		
Pelvic lymph node involvement			22.00 (7.36-65.81)	< 0.01
No	176 (96)	8 (4)		
Yes	11 (50)	11 (50)		

PI: parametrial involvement, OR: odds ratio, CI: confidence interval, SD: standard deviation

Table 3. Multivariate analysis of risk factors for parametrial involvement.

Characteristics	OR (95%CI)	p value
Stage	0.307 (0.00 – 101.49)	0.69
Stromal invasion	10.075 (1.35 – 75.14)	0.02
Tumor size	2.659 (0.01 – 989.49)	0.75
Lymphovascular space invasion	2.254 (0.55 – 9.28)	0.26
Pelvic lymph node involvement	10.627 (3.21 – 35.17)	<0.01

OR: odds ratio, CI: confidence interval

Discussion

In the present study, PI was found in 9.22% of patients with stage IA2-IIA1 cervical cancer. This result was comparable to previous reports in the literature with the incidences of PI ranging from 4 to 11%[5-6, 9-12]. The somewhat high incidence of PI in our study might be attributed to the larger tumor size (> 4 cm) in some of our patients. Furthermore, our series included patients with stage IIA1 disease, while the diseases higher than stage IB2 were excluded in other studies[6, 9].

Our results demonstrated that tumors size > 2 cm, DSI > 10 mm or invasion > 50% of the whole cervical thickness, positive LVSI, or pelvic lymph node involvement were associated with PI. These results were in line with those previously reported in other studies[5, 6, 9]. However, pelvic lymph node status and DSI were the only two independent factors associated with PI after adjusting the confounding factors by multivariate analysis. Notably, none of the participants with stromal invasion < 10 mm, less than one-third stromal invasion, or negative pelvic lymph node involvement had PI.

There has been no standard cut-off level for DSI. Several studies used 10 mm of DSI as their reference[7, 10, 13], However, the absolute depth of tumor invasion may be affected by the anatomical differences among the patients. The Gynecologic Oncology Group (GOG) study proposed the use of the proportion between the depth of the lesion and entire cervical thickness[14]. The invasion of more than one-third of the whole thickness, which reflected the intermediate risk for disease recurrence, was used as a cut-off level for DSI in our study which was in concordance with the GOG study. The problem of using DSI prior to the surgery to omit radical hysterectomy is that the preoperative DSI assessment is not routinely performed. Although, loop electrosurgical excision procedure (LEEP) can provide some information regarding DSI, the treatment delay makes it not suitable for most of the patients with cervical cancer. The imaging with either ultrasonography or magnetic resonance imaging (MRI) has been evaluated in some studies for preoperative DSI evaluation[15], However, the accuracy and cost-effectiveness of these techniques were still questioned. Pelvic node status was also an independent factor associated with PI in this study. Only 4% (8/184) of patients without pelvic lymph node involvement had PI, while 50% (11/22) of those with pelvic lymph node metastasis had disease involving parametrium ($p < 0.01$). Our findings were consistent with another previous report[7]. Pelvic lymph node involvement can be accurately evaluated prior to radical hysterectomy using intraoperative frozen section via laparoscopy or exploratory laparotomy. The pelvic lymph node status and preoperative DSI may provide information for decision making of a proper surgical procedure or choosing other treatment modalities[16].

It is advisable to identify a subgroup of patients with low-risk for PI. These patients can be offered the DSI assessment by transvaginal ultrasonography, MRI, or pathologic result from the LEEP specimen and intraoperative evaluation of pelvic lymph node status by frozen section before a definite surgical procedure was performed. Since radical hysterectomy is still the standard treatment for non-bulky early-stage cervical cancer, therefore, less radical surgery for patients who have low-risk for PI should be considered only in the setting of clinical trials. Future studies focusing on the benefit of identifying some patients with cervical cancer who are suitable for less radical surgery in term of decreasing surgical complications without compromising the oncologic outcomes is still warranted.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143:22-36.
2. Sangariyavanich E, Buasom R. Hospital-based cancer registry. Bangkok: New Thammada Press 2018:1-4.
3. Jiamset I, Hanprasertpong J. Risk factors for parametrial involvement in early-stage cervical cancer and identification of patients suitable for less radical surgery. Oncol Res Treat 2016;39:432-8.
4. Hacker NF, Vermorken JB. Cervical cancer. In: Berek JS,

Hacker NF, editors. Berek & Hacker's gynecologic oncology. 6th ed. Philadelphia: Wolters Kluwer 2015:326-89.
5. Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, et al. Utility of parametrectomy for early-stage cervical cancer treated with radical hysterectomy. Cancer 2007;110:1281-6.
6. Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstet Gynecol 2009;114:93-9.
7. Vanichtantikul A, Tantbirojn P, Manchana T. Parametrial involvement in women with low-risk, early-stage cervical cancer. Eur J Cancer Care 2017;26:1-5.
8. Cohen J. A power primer. Psychol bull 1992;112:155-9.
9. Kodama J, Kusumoto T, Nakamura K, Seki N, Hongo A, Hiramatsu Y. Factors associated with parametrial involvement in stage IB1 cervical cancer and identification of patients suitable for less radical surgery. Gynecol Oncol 2011;122:491-4.
10. Baiocchi G, de Brot L, Faloppa CC, Mantoan H, Duque MR, Badiglian-Filho L, et al. Is parametrectomy always necessary in early-stage cervical cancer? Gynecol Oncol 2017;146:16-9.
11. Dabi Y, Willecocq C, Ballester M, Carcopino X, Bendifallah S, Ouldamer L, et al. Identification of a low risk population for parametrial invasion in patients with early-stage cervical cancer. J Transl Med 2018;16:163-72.
12. Xie X, Song K, Cui B, Jiang J, Zhang Y, Wang B, et al. Significance of the factors associated with parametrial involvement in stage IB to IIA cervical cancer. Int J Gynecol Cancer 2016;26:939-43.
13. Lee SH, Cho KJ, Ko MH, Cho HY, Lee KB, Lim S. Factors associated with parametrial involvement in patients with stage IB1 cervical cancer: Who is suitable for less radical surgery? Obstet Gynecol Sci 2018;61:88-94.
14. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. Gynecol Oncol 1999;73:177-83.
15. Epstein E, Testa A, Gaurilcikas A, Di Legge A, Ameye L, Atstupenaite V, et al. Early-stage cervical cancer: Tumor delineation by magnetic resonance imaging and ultrasound - A European multicenter trial. Gynecol Oncol 2013;128:449-53.
16. Reade CJ, Eiriksson LR, Covens A. Surgery for early stage cervical cancer: how radical should it be? Gynecol Oncol 2013;131:222-30.

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GYNAECOLOGY

The Appropriate Time for Cytology Examination to Screen for Cervical Cancer after Childbirth

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ABSTRACT

Objectives: To compare the rate of satisfactory Pap smear for postpartum checkup between at 6th and 8th week.

Materials and Methods: This was a randomized controlled trial study. The data were collected from the participants who came to postpartum clinic at the 6 and 8 weeks after childbirth in Phrapokklao hospital from February to May 2020. Satisfactory specimen was evaluated as defined by Bethesda reporting system (2014).

Results: The participants (144) who came for examination at 6 and 8 weeks after childbirth were divided into two groups. First group of 72 participants was at 6 weeks postpartum and the second group of 72 participants was at 8 weeks postpartum. From the results, 17 participants (23.6%) with vaginal bleeding were found in the first group, while only 2 (2.7%) in the second group. For the satisfactory of the specimen, the second group had no vaginal bleeding and showed more satisfactory specimen for cytologic screening of cervical cancer result than the participants in the first group (70 (97.3%) vs 55 (76.4%)). The difference between the two groups were statistical significance ($p < 0.001$).

Conclusion: Timing of postpartum checkup at 8th week was appropriate than at 6th week because of less vaginal bleeding and showed more satisfactory of cytologic screening for cervical cancer. Changing the period of appointment to the same as her neonatal vaccine program schedule also might get benefit from decreasing expense and number of hospital visit.

Keywords: postpartum pap smear, time for postpartum care.

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ระยะเวลาเหมาะสมต่อการตรวจเซลล์วิทยาเพื่อคัดกรองมะเร็งปากมดลูกหลังคลอด

ณัฐวดี ศรีแสนยงค์, ชุลีกร ศรีตนไชย

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบสเมียร์ที่สามารถให้การแปลผลทางเซลล์วิทยาของการตรวจคัดกรองมะเร็งปากมดลูก ในช่วงสัปดาห์ที่ 6 และ 8 หลังคลอด*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่มที่มีกลุ่มควบคุม เก็บรวบรวมข้อมูลของหญิงหลังคลอดที่มาตรวจที่คลินิกหลังคลอดที่ระยะเวลา 6 และ 8 สัปดาห์ภายหลังคลอด ระหว่างเดือนกุมภาพันธ์ ถึงพฤษภาคม พ.ศ.2563 โดยที่ความสามารถในการให้การแปลผลทางเซลล์วิทยาของการตรวจคัดกรองมะเร็งปากมดลูกพิจารณาตามกำหนดของ Bethesda System 2004*

ผลการศึกษา: *มีหญิงหลังคลอดจำนวน 144 คน ที่เข้าร่วมในงานวิจัย โดยแบ่งออกเป็นสองกลุ่ม คือกลุ่มแรกถูกนัดมาตรวจใน 6 สัปดาห์ และ กลุ่มที่ 2 ถูกนัดมาตรวจที่ 8 สัปดาห์หลังคลอด มีผู้เข้าร่วมงานวิจัยในกลุ่มแรกจำนวน 72 คน เช่นเดียวกับในกลุ่มที่สอง จากผลการวิจัยพบผู้เข้าร่วมวิจัย 17 คน (ร้อยละ 23.6) ในกลุ่มที่นัดมาตรวจที่ 6 สัปดาห์หลังคลอดมีเลือดออกทางช่องคลอดในขณะที่พบเพียง 2 คน (ร้อยละ 2.7) ในกลุ่มที่สอง เมื่อพิจารณาในเรื่องความเหมาะสมของสิ่งส่งตรวจเพื่อคัดกรองมะเร็งปากมดลูกพบว่า กลุ่มที่สองที่ไม่มีเลือดออกทางช่องคลอดมีคุณภาพของสิ่งส่งตรวจที่น่าพอใจมากกว่ากลุ่มแรก (70 (ร้อยละ 97.3) vs 55 (ร้อยละ 4)) ความแตกต่างระหว่างทั้งสองกลุ่มมีนัยสำคัญทางสถิติ ($p < 0.001$)*

สรุป: *การนัดตรวจหลังคลอดในสัปดาห์ที่ 8 มีความเหมาะสมกว่าที่ 6 สัปดาห์หลังคลอด เนื่องจากพบมีเลือดออกทางช่องคลอดน้อยกว่า และพบว่ามีคุณภาพที่ดีกว่าของสิ่งส่งตรวจเพื่อคัดกรองทางเซลล์วิทยาสำหรับมะเร็งปากมดลูก การเปลี่ยนระยะเวลาการนัดหมายให้เหมือนกับตารางโปรแกรมวัคซีนทารกแรกเกิดอาจได้รับประโยชน์จากค่าใช้จ่ายที่ลดลงและลดจำนวนครั้งของการมาโรงพยาบาล*

คำสำคัญ: *การคัดกรองมะเร็งปากมดลูกหลังคลอด, ช่วงเวลาของการตรวจหลังคลอด*

Introduction

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) (2017) recommended that the examination should be operated within 4 to 6 weeks after giving birth in order to monitor postpartum symptoms, plan for contraception, monitor and prevent mothers' complications after delivery[1]. There were many postpartum complications reported within 8 weeks after delivery such as fatigue (59%), breast problem (36%), anemia (25%), backache (24%), hemorrhoids (23%), headache (22%), postpartum blue (21%), constipation (20%), suture breakdown (20%) and abnormal vaginal discharge (15%)[1, 2]. The rate of complication was remained the same and acceptable for examination within 8 weeks period but there was no data about the complication beyond 8 weeks postpartum. Furthermore, the standard Thai vaccination for the babies were 2 months after birth that it can make the appointment for mother together with her child[3].

According to the optimizing postpartum care, ACOG (2018) recommends the appointment for the examination of postpartum mothers could be scheduled from 3 to 12 weeks after childbirth delivery in order to evaluate psychological well-being[1, 2]. The evaluation included: mood and emotional well-being; infant care and feeding; sexuality, contraception and birth spacing; sleep and fatigue; physical recovery from birth; chronic disease management; and health maintenance[1]. The examination for cervical cancer screening after giving birth is one of the health maintenance domains. Previous studies were found that the incidence of abnormal cervical cells detection in pregnant and postpartum mothers was 5-8%[4, 5], and the incidence of cancer among pregnant women in the period of 12 months after delivery was 13.5%[6, 7]. In addition, one study has shown that abnormal pap smear occurred in the postpartum women who previously showed normal result before pregnancy was 4.9%[8, 9]. Therefore, cervical cancer screening after giving birth is essential and should encourage in every postpartum woman.

At the postpartum clinic of Phrapokklao Hospital, we assigned the appointment to every postpartum mother for examining and monitoring abnormal symptoms after delivery. Moreover, plan for contraception and cytologic screen for cervical cancer were performed at the same time. In general, the appointment would be scheduled at the 6 weeks after childbirth. However, the problem was the postpartum womens who scheduled to attend at the 6th week had vaginal bleeding (without any infections or complications). As we knew that blood could obscure the cytology result. So, the 6-week postpartum might not be suitable time for examination[10]. From the scope of view, this study aimed to postpone the postpartum appointment to another next two weeks to perform the checkup program. Rate of vaginal bleeding and satisfactory of cytologic specimen for cervical cancer were evaluated compare between conventional standard appointment and the extended period.

Materials and Methods

The research was randomized controlled trial. The population were women who came for postpartum examination at 6 and 8 weeks after delivery between February and May 2020. The inclusion criteria were Thai, age > 18 years old, completed informed consent, childbirth at Phrapokklao hospital. Foreigner, lack of understanding in Thai language, and who planned to follow-up at other hospital were excluded. Primary outcome was rate of satisfactory Pap smear specimen between 6 and 8 weeks postpartum. The sample size was calculated from clinical observation at 6 weeks after delivery (standard appointment). In the clinical observation of 13 people, 5 participants were unable to screen for cervical cancer due to vaginal bleeding. Therefore, the proportion was 0.62 that Pap smear can be done. In conjunction with the reference study, it was 100% proportion of biopsies, that were appropriate for examination at 8 weeks after delivery[11]. The power of a test was set at 0.9. Then, calculation from the formular was used.

$$n\ per\ group = \frac{2(z_\alpha + z_\beta)^2 p(1-p)}{(pT - p_C)^2_{..}}$$

The research was approved by human research ethics considerations, Chanthaburi Province / Health Zone 6, Project No. CTIREC 001/63. The sample size was 144 participants and additional with 10% loss follow up. Thus, the final number of sample size was 159 participants that divided into 2 groups (Fig. 1). The appointment was scheduled at 6 weeks and 8 weeks period. The standard checkup program was consisted of taking personal history, physical examination and pelvic examination to rule out abnormal uterine bleeding. Screening for cervical cancer with conventional Pap smear method were done by obstetrician on duty. The Pap smear specimens were sent for interpretation by one pathologist. Satisfactory for evaluation was depend on the presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., partially obscuring blood, inflammation as defined by Bethesda reporting system (2014)[10].

The standard examination composed of 5 steps as follows: 1) Setting the patient on lithotomy position for pelvic examination, 2) Preparing equipment such as set flush for cleaning, speculum, Ayre spatula, etc., 3) After cleaning, applying the speculum passing through vaginal canal and identifying the cervix, 4) Using both sides of Ayre spatula by inserting into the cervix then rotating 360° for two complete rounds, 5) Smearing the collected specimen on slide then fix cell in 95% ethanol before sending to the pathologist.

The data were collected from medical history recording including age, weight and height calculated for body mass index (BMI), mode of delivery, infant weight after birth, term, breastfeeding after childbirth, birth complications, history of cervical surgery, cervical infection, and postpartum bleeding on the follow-up date.

Statistical Analysis

The data were analyzed by chi square statistics using SPSS Version 26 to compare between groups. The statistically significant difference of p value was less than 0.05.

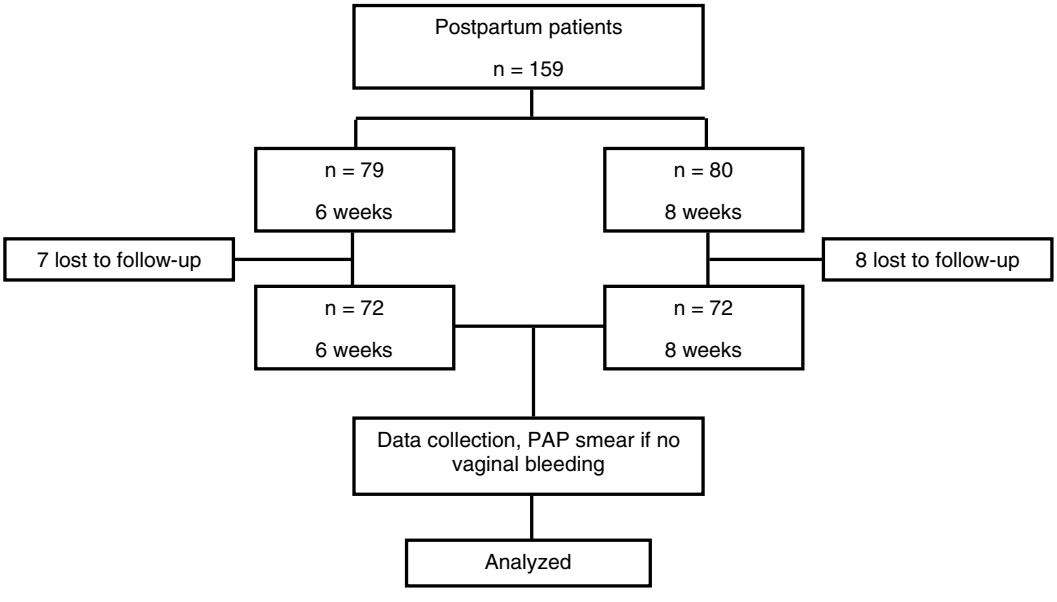

Fig. 1. The chart of population groups collection.

Results

The 159 participants were selected at the postpartum ward and randomly divided in 2 groups of appointment, at 6 and 8 weeks postpartum. At

time of the appointment, the participants who lost to follow-up were 7 and 8 in first and the second group, respectively. So, there were 72 participants in each group. The study was implemented by comparing the difference in proportions of characteristics between the two groups (Table 1). Although the 6-week group showed more case of term pregnancy, younger age and more case of successful breast feeding, it was not showed any statistical difference. Also, there were no statistical differences between BMI, neonatal birth weight and mode of delivery.

Table 1. Demographic and characteristic of the participants studied.

Characteristic	Schedule of appointment		p value
	6th week (n = 72)	8th week (n = 72)	
Age (years)	27.3 ± 6.3	28.2 ± 5.7	0.379
BMI (kg/m²)	24.3 ± 4.4	24.1 ± 4.1	0.731
Birth weight (grams)	2,926.4 ± 424.1	2,920.6 ± 278.5	0.923
Mode of delivery, n (%)			0.632
Normal delivery	41 (56.9)	46 (63.8)	
Cesarean section	29 (40.2)	25 (34.7)	
Vacuum extraction	2 (2.9)	1 (1.5)	
Term, n (%)	69 (95.8)	65 (90.2)	0.189
Preterm, n (%)	3 (4.2)	7 (9.8)	
Parity, n (%)			0.667
1	35 (48.6)	28 (38.8)	
2	29 (40.2)	33 (45.8)	
3	7 (9.7)	10 (13.8)	
4	1 (1.5)	1 (1.6)	
Breast feeding, n (%)			0.085
Yes	70 (97.2)	65 (90.2)	
No	2 (2.8)	7 (9.8)	
Complications, n (%)			0.460
Yes	11 (15.2)	8 (11.1)	
PPH (%)	0	12.5	
GDM (%)	72.7	75	
GHT (%)	18.1	12.5	
CHT (%)	0	0	
PROM (%)	9.2	0	
No	61 (84.8)	64 (88.9)	
Cervical infection, n (%)			0.559
Yes	1 (1.4)	2 (2.7)	
No	71 (98.6)	70 (97.3)	
Prior cervical surgery n (%)			0.559
Yes (MVA)	1 (1.4)	2 (2.7)	
No	71 (98.6)	70 (97.3)	

PPH: postpartum hemorrhage, GDM: gestational diabetes mellitus, GHT: gestational hypertension, CHT:chronic hypertension, PROM: premature rupture of membranes, MVA: manual vacuum aspiration.

Other risk factors and intrapartum complications such as postpartum hemorrhage, gestational diabetes mellitus, gestational hypertension, chronic hypertension, and premature rupture of membranes, cervical infection, prior cervical surgery showed no difference in statistical significance level ($p > 0.05$).

Participants whose showed vaginal bleeding was found 17 (23.6%) in the 6 weeks postpartum group compared to 2 (2.7%) in the 8 weeks postpartum group (Table 2).

The participants who had no vaginal bleeding and showed satisfactory Pap smear specimen were 55 (76.4%) in the 6 weeks postpartum group and 70 (97.3%) in the 8 weeks postpartum group. The difference in proportion between the two groups were significantly difference ($p < 0.001$) (Table 2).

Table 2. Analysis of proportional differences of satisfied Pap smear specimen between 6th and 8th week postpartum period.

Outcomes	Schedule of appointment		p value
	6th week (n = 72)	8th week (n = 72)	
Bleeding per vagina, n (%)	17 (23.6)	2 (2.7)	< 0.001
Satisfactory Pap smear specimen, n (%)	55 (76.4)	70 (97.3)	

* p value ≤ 0 .05

Discussion

Postpartum checkup is a medical schedule program that women get after childbirth to make sure they recovered well from labor and birth. Postpartum care is important because new mothers were at risk of serious and sometimes life-threatening health complications as mentioned previously[1, 2]. The time for postpartum is varied from 4 to eight weeks postnatal. By the time the reproductive organs should return to its pre-pregnancy status. Postpartum checkup is practiced by general assessment to reassure woman that she was well and coping with the early transition to motherhood. The program consisted of many aspects including physical examination, emotional support, contraception and breastfeeding support. Screening for cervical cancer in essential especially in developing country because the incidence of it was still high.

Papanicolaou smear is a conventional screening for cervical cancer. Although it was widely used worldwide especially in developing country. The sensitivity was only 51% and false negative rate was 49%[12]. One of the major pitfalls was from the inadequate specimen collection[13].

Postpartum bleeding is divided to three stages[1]. Lochia rubra is at days 2-4. Lochia serosa is at day 4 and lasts about 2 weeks. While lochia alba is from 2 to 6 weeks postpartum. Lochia alba is light yellow or yellowish white in color, with the bleeding virtually gone. It should smell like regular menstrual blood and no blood clots. If at the time of standard appointment for postpartum checkup, bleeding may be from menstruation or some type of infection because the shortest days after delivery to ovulation is 42 days[14].

The result showed that the incidence of vaginal bleeding at 8 weeks postpartum was less than 6 weeks postpartum. Also, in the 8 weeks postpartum, it showed more quality of cytologic specimen collected for cervical cancer. Therefore, the differences in proportions between two groups of vaginal bleeding were analyzed and showed that the different proportions were significantly ($p < 0.001$).

The prior study result: "Postpartum cervical cancer screening adequacy and results: comparison of results 2-3 versus 6-8 weeks postpartum" suggested that the rate of cytologic adequacy in the breastfeeding groups who had 6-8 weeks postpartum follow-up appointments was found more than those of 2-3 weeks postpartum. The finding supports our results, but the

our study was to specifically distinguish timing between 6 and 8 weeks.

The other advantage of this research was in economical aspect. Some participants[18] in the 8 weeks postpartum group had appointments with the pediatrician with their children to follow-up after birth and received vaccination at 2-month-old (8 weeks postpartum). Those included diphtheria, tetanus, and pertussis vaccine, oral polio vaccine and other complementary vaccines such as rotavirus vaccine (Rota 1) and pneumococcal vaccine[15, 16]. We suggest that mothers should be scheduled for examination and together with their children at 8 weeks postpartum. This may decrease hospital visit rate, expenses, and increase working time of the patients. The strength of this research was randomized controlled trial study with standardized examiners, and technique. The limitation of this research was no calculation about the cost and value of the program. Furthermore, vaginal bleeding may obscure the interpretation from conventional Pap smear but not the liquid-based cytology. Further appropriate research should be planned in the future.

Conclusion

In conclusion, timing of postpartum checkup at 8th week was appropriate than at 6th week because of less vaginal bleeding and showed more satisfactory of cytologic screening for cervical cancer. Changing the period of appointment to the same as her neonatal vaccine program schedule also might get benefit from decreasing expense and number of hospital visit

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BL, et al. Williams Obstetrics. 25th ed. New York: Mc Graw Hill 2018: 652-65.
2. McKinney J, Keyser L, Clinton S, Pagliano C. ACOG Committee opinion no. 736: optimizing postpartum care. Obstet Gynecol 2018;132:784-5.
3. Schuchat A, Anderson LJ, Rodewald LE, Cox NJ, Hajjeh R, Pallansch MA, et al. Progress in Vaccine-Preventable and Respiratory Infectious Diseases-First 10 Years of the CDC National Center for Immunization and Respiratory Diseases, 2006-2015. Emerg Infect Dis 2018;24:1178-87.
4. Weiss BD, Senf JH, Udall W. The postpartum Papanicolaou smear. J Am Board Fam Pract 1989;2: 4-9.
5 Rarick TL, Tchabo JG. Timing of the postpartum Papanicolaou smear. Obstet Gynecol 1994;83:761-5.
6. Smith LH, Dalrymple JL, Leiserowitz GS, Danielsen B, Gilbert WM. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. Am J Obstet Gynecol 2001;184:1504-12.
7. Paladine, HL, Blenning CE, Strangas Y. Postpartum care: an approach to the fourth trimester. Am Fam Physician 2019;100:485-91.
8. Bond S. Caring for women with abnormal papanicolaou tests during pregnancy. J Midwifery Womens Health 2009;54: 201-10.
9. Suzuki K, Furuhashi M, Kawamura T, Kubo M, Osato K, Yamawaki T. Comparing Papanicolaou test results obtained during pregnancy and post-partum. J Obstet Gynaecol Res 2017;43:705-9.
10. Nayar R, Wilbur DC. The pap test and Bethesda 2014. Acta Cytologica 2015;59:121-32.
11. Carty J, Batig A. Postpartum cervical cancer screening adequacy and results: comparison of results 2-3 versus 6-8 weeks postpartum. Obstet Gynecol 2017;129: 57S.
12. McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, et al. Evaluation of cervical cytology. Evidence Report/Technology Assessment No.5 (Prepared by Duke University under Contract No. 290-97-0014.) AHCPR Publication No. 99-E010. Rockville, MD: Agency of Health Care Policy and Research 1999.
13. Fetherston WC. False negative cytology in invasive cancer of the cervix. Clin Obstet Gynecol 1983;26:929-37.
14. Jackson E, Glasier A. Return of ovulation and menses in postpartum nonlactating women: a systematic review. Obstet Gynecol 2011;117:657-62.
15. Demirjian A, Levy O. Safety and efficacy of neonatal vaccination. Eur J Immunol 2009;39:36-46.
16. Kelly H, Jacoby P, Dixon GA, Carcione D, Williams S, Moore HC, et al. Vaccine effectiveness against laboratory-confirmed influenza in healthy young children: a case control study. Pediatr Infect Dis J 2011;30:107-11.