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7. encourage and being aware of research into peer review and publishing and reassessing the journal's processes in the light of new findings.

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EDITORIAL

This fourth issue of Thai Journal of Obstetrics and Gynaecology (TJOG) contains many interesting articles. The special article in this issue is "**Cannabis (Gan-ja): Relevant Issues in Obstetrics and Gynecology**"

We already announced the best paper award of TJOG 2017 at RTCOG Annual Meeting 2018 at Khao Yai Convention Center, Nakornraschasima. The best paper was "**Efficacy of Topical Ethyl Chloride Spray versus Subcutaneous 1% Lidocaine Injection in Reducing Pain from One Rod System Implant Insertion**"

Editor in Chief and managing staff attended the Thai-Journal Citation Index meeting: "**Selection and categorization criteria for the 4th round re-evaluation for TCI indexed journals (2020-2024)**" at Ambassador Hotel, Bangkok on September 28, 2018. Next year, TJOG will be changed for preparing the journal according to the new criteria for re-evaluation to be index in TCI journals (2020-2024). Editorial Board of TJOG look forward to continuously raising the quality of the TJOG and prepare journal for submission to be index in Scopus index.

For the coming New Year 2019, we would like to extend our warmest wishes to RTCOG members, editorial board, reviewers, authors and families. We thank to all the authors, readers, reviewers, and editors for your contributions to TJOG this past year.

Warmest greetings and best wishes for the new year 2019.

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

Thai Journal of Obstetrics and Gynaecology
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SPECIAL ARTICLE

Cannabis (Gan-ja): Relevant Issues in Obstetrics and Gynecology

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ABSTRACT

Medical benefits of cannabis have become widely accepted. In Obstetrics and Gynecology, it was reported to be useful to alleviate nausea and vomiting from morning sickness in pregnant women and in gynecologic cancer patients who received chemotherapy. It has also been used as a pain killer during labor and menstruation. Some also claimed that the cannabis may also prolong life of cancer patients or even cure cancer. Owing to the illegalization of the cannabis in many countries for a long time, there has been no evidence-based data from clinical study to support the use of cannabis for those aforementioned conditions except for chemotherapy induced nausea/vomiting. Systematics reviews confirmed that cannabis was significantly more effective than placebo and at least as effective as various conventional antiemetics. However, due to the availability of many potent new standard antiemetics (5-HT3 receptor antagonists, and neurokinin-1-receptor-antagonists) without psychotropic effects, cannabis is not recommended as a first-line antiemetic agent. The exception is when the new standard antiemetics cannot adequately control nausea and vomiting from chemotherapy. The cannabis is contraindicated in pregnant women or lactating mother because of the possibility of adverse fetal and neonatal outcomes. Once cannabis is legalized for medical use in more countries, its efficacy in those aforementioned conditions can be tested and confirmed in randomized controlled trials.

Keywords: cannabis, marijuana, obstetrics, gynecology, pregnancy, cancer.

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Why should we know about cannabis?

Although cannabis is considered an illegal drug in Thailand due to its possible harmful effects on health, its medical benefits are widely accepted. At present, medical cannabis is legal in many countries and possibly in Thailand in 2019.

Cannabis, generally known as “marijuana” or local name “gan-ja”, has long been used for recreational and medical purposes. The Ancient Greeks used cannabis to dress wounds. Dry leaves of cannabis were used to treat nosebleed and its seeds were used to expel tapeworms[1]. Queen Victoria of Britain was also

claimed to have been prescribed cannabis for her menstrual pain and during childbirth[2].

Cannabis is one common ingredient in many Thai traditional medicine recipes as written in King Narai Pharmaceutical textbook and on the stone at Wat Phrachetupon Wimonmangkararam (Wat Pho). In the past, Thailand was famous for having the best strains of cannabis and as one of the top exporters of cannabis in the world[3].

In Thailand, cannabis has been grouped in category 5 narcotics under Narcotics act 1979. The production, sale or possession of any form of cannabis is illegal. The punishment varies from fine to imprisonment. This act results from the international drug control treaty as a part of the World War I peace treaties in 1912, which led to the national drugs control acts in most countries[4].

Since the early 20th century, advance in medical knowledge about cannabis makes the legal status of cannabis change rapidly. As of now, many countries have legalized the medical use of cannabis (such as Australia, Canada, Chile, Colombia, Germany, Greece, Israel, Italy, Netherlands, Peru, Poland, etc.). Moreover, some countries (Uruguay, Canada, Spain, etc.) have also legalized cannabis for recreational use.

In the United States of America, although whole or crude marijuana is not approved by the US Food and Drug Administration (FDA) for any medical use, pharmaceutical forms of cannabis product are approved by the FDA to treat some conditions[5]. Besides, medical marijuana is legal under state laws in around 30 states all over the country, such as California, New York, Illinois, Maryland, Massachusetts, Pennsylvania, Washington DC, etc. On the other hand, recreational marijuana is legal in around 10 states including California, Massachusetts, Washington DC, etc[6].

In Thailand, the narcotic law has been under revision process. Once this new regulation is approved (may be early next year; 2019), cannabis will be allowed for medical use in humans. As of now, Thailand's Governmental Pharmaceutical Organization (GPO) is contemplating researches to develop medicines from cannabis. A project to develop a special greenhouse to grow the premium-grade cannabis for researches is underway. They are waiting for the legalization to do the research of medical cannabis in humans.

What are cannabis and cannabinoid?

Cannabis is a kind of plant that has 2 major active components: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has psychoactive effect while CBD has anti-inflammatory, antioxidant, and neuroprotective effect. Cannabinoid is a group of chemical compounds that either are derived from the cannabis plant (phytocannabinoids), are synthetic analogues (synthetic cannabinoids), or occur endogenously (endocannabinoids). Synthetic cannabinoids that are currently in clinical use include Dronabinol (oral synthetic THC) and Nabilone (oral synthetic THC).

Cannabis is a flowering plant in the family Cannabaceae. It is originated in Central Asia, but now is cultivated worldwide, including Southern Asia, India, Middle East, Africa, Europe, Canada and the Americas. The main species are Cannabis sativa, followed by Cannabis indica, and Cannabis ruderalis.

The term 'cannabis' is a scientific term or generic term that encompasses the compound as used in its herbal form, resin form, and in various derived or synthesized cannabinoid products[7]. Cannabis has many names such as marijuana (or marihuana), ganja (ganga), herb, bud, grass, pot, dope, Mary Jane, hooch, weed, hash, joints, brew, reefers, cones, smoke, mull, buddha, hydro, yarndi, Purple Haze, Northern Lights, charas, skunk, resin, heads and green[8-10]. Marijuana is usually referred to dried flowers and leaves of the cannabis plants[8], while other names are the slang names which in part reflect variations in genetics, growing conditions, processing, and constituent cannabinoids and other chemical compounds in different strains of the plants[10].

Endocannabinoids are fatty-acid cannabinoids produced naturally in the body[11]. The endocannabinoid system (ECS) is a physiologic system which regulates

various basic functions in human body, such as appetite, metabolism, sleep, mood, immune function, inflammation, neuronal development and protection, digestion, reproduction, memory, and learning, etc[12]. Cannabinoids interact mostly at cannabinoid receptors, but might have cross activity with opioid receptors[13]. Currently, two cannabinoid receptor subtypes have been identified: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2)[11]. CB1 functions to modulate neurotransmitter activity in the brain, which can influence nausea, muscle spasticity, seizures, and psychoactivity[11]. CB2 receptors are expressed mainly outside the brain such as in cells and organs of the immune system and their regulatory functions[11].

Phytocannabinoids are cannabinoids that occur naturally in the cannabis plant. Two major active cannabinoids are Δ9 - tetrahydrocannabinol (THC) and cannabidiol (CBD)[10]. The THC can acutely impair learning and produce euphoria (high), schizophrenia-like symptoms, and anxiety[14], whereas CBD can enhance learning and has anti-inflammatory, antioxidant, neuroprotective, antipsychotic and anti-anxiety effects[15-17]. When taken together, the CBD may counteract and decrease adverse effects of THC[18]. Nabiximols and Epidiolex are the pharmaceutical products from cannabis plants that are currently, in clinical use.

Nabiximols (Sativex), an oromucosal spray containing THC and CBD in a 1:1 ratio, is an extract of cannabis used to treat cancer pain as well as muscle spasms and pain from multiple sclerosis[5,19].

Cannabidiol (Epidiolex), an oral solution CBD made from cannabis, is licensed for the treatment of two forms of severe childhood epilepsy, Dravet syndrome and Lennox-Gastaut syndrome[5].

Synthetic cannabinoids are cannabinoids that are synthesized in a laboratory. Synthetic cannabinoids that are currently in clinical use included Dronabinol and Nabilone[5,19].

Dronabinol (Marinol), an oral capsule containing synthetic THC, is licensed for treatment of anorexia as well as weight loss in patients with AIDS and chemotherapy induced nausea and vomiting[5,19].

Nabilone (Cesamet), an oral capsule containing synthetic cannabinoid derivative mimicking THC, is approved for chemotherapy-induced nausea and vomiting that was not responded to conventional antiemetics[5,19].

What are the preparations and route of cannabis administration?

There are many forms of cannabis such as herbal form, resin form, tincture, oil and synthesized cannabinoid products. Herbal form varies greatly based on strain, growing conditions, and processing. Patients who use this form may have to titrate their cannabis intake. Cannabis can be used by smoking, vaporizing, oral intake, oral spray, oral drop, suppositories or topically use.

Cannabis in the raw plant is in an acid form - tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) which do not interact with the human body. THCA and CBDA must be heated to decarboxylate the acid to THC and CBD to make them available for use in the human body[11].

There are many forms of cannabis such as herbal form, resin form, tincture, oil and synthesized cannabinoid products. The components of chemical compounds in cannabis plants vary greatly based on strain, growing conditions, and processing[10,11]. Besides, individual responses to cannabis may be different and unpredictable[20]. Each patient or consumer may prefer one form over another. Some patients may prefer synthetic cannabinoids because of their consistency whereas some may prefer cannabis plants. This may be because cannabis plant is a blend of many different natural cannabinoids and terpenes. Each compound has its own individual effects, but it may be more effective when work together (entourage effect). Hence, the patients who use natural cannabis plant for medical purpose may have to titrate their cannabis intake.

Cannabis can be consumed by several means: smoking, vaporizing, oral intake, oral spray or drop, suppositories or topically use[21,22]. The most common

of which are rolling it into cigarettes or putting it in a pipe or in a cigar for smoking. It can be mixed with food (such as brownies, cakes, butter, candy, ice cream, chewing gum, etc.), or made into tea, juice, smoothies, etc[21-23]. It can also be administered sublingually as spray or tincture drop[21,22]. It can be used as vaginal or rectal suppositories, which mostly made from cannabis-infused coconut oil or cocoa butter-base[11]. It can also be used as topical oil emollient on the skin. Of these, smoking provides most rapid onset of effects within minutes and lasts for 2-4 hours while the onset of oral intake is about 60 to 180 minutes and lasts for 6-8 hours[21].

Why should obstetricians and gynecologists know about cannabis?

Medical cannabis may be useful in both obstetrical and gynecological practices. It may be used as an antiemetic agent in gynecologic cancer patients receiving chemotherapy and in pregnant women for morning sickness, as pain killer for menstrual cramp and labor pain. However, one important caveat of cannabis use in pregnant women is the adverse effect on fetus.

The use of cannabis in obstetrics and gynecology has been recorded as early as 2737 BCE. It has been used for treatment of menstrual cramp, labor pain and even induction of labor. As of now, medical evidences have suggested the benefit of cannabis in relieving various symptoms of nausea/vomiting, chronic pain, spasticity in multiple sclerosis (MS), depression, anxiety disorder, sleep disorder, etc. However; according to a recent systematic review and meta-analysis by Whiting et al[9], there was only moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity, and low-quality evidence suggesting the improvements in chemotherapy induced nausea and vomiting, weight gain in HIV infection and sleep disorders. At present, a few indications have been widely accepted, which include pediatric treatment-resistant epilepsy (especially Dravet syndrome and Lennox-Gastaut syndrome), pain syndromes associated with multiple sclerosis and chemotherapy-induced nausea[24].

Since medical evidences support the use of cannabis for pain and nausea, questions arise for its efficacy for nausea and vomiting from morning sickness syndrome and for labor pain. One precaution is when the cannabis is available as an over-counter drug or even with physician prescription; there may be more pregnant patients use them for leisure or recreation. Therefore obstetricians should know whether cannabis is safe for the fetus in utero. Gynecologists also should know whether cannabis could help women who suffer from menstrual pain or dysmenorrhea. Gynecologic oncologist should know whether cannabis products are better than standard antiemetics for gynecologic cancer patients who receive chemotherapy, and whether cannabis should cure cancer.

Is cannabis useful in nausea/vomiting of pregnancy (morning sickness to hyperemesis gravidarum)?

There has been no evidence-based data of cannabis as an antiemesis in nausea/vomiting of pregnancy. To date, only some case reports and survey studies claim its effect in nausea/vomiting of pregnancy and even hyperemesis gravidarum.

Historically, cannabis has been utilized as a treatment for morning sickness[25]. There were few case reports and survey studies that reported the use of cannabis in treatment of nausea/vomiting of pregnancy and even hyperemesis gravidarum. A case study by Curry[26] demonstrated that nausea and vomiting of pregnancy may be relieved by smoking cannabis in very small amount (1-2 puffs, 1-2 times a day). In 2009, Westfall et al[27], reported his survey of 79 female users of medicinal cannabis who had experienced pregnancy. Of those 40 who used cannabis to treat nausea and/or vomiting of pregnancy, 37 (over 92%) rated cannabis as extremely effective or effective.

To date, there has been no study actually assessed its efficacy for this indication. Prospective studies or good clinical trials are needed to confirm its

effectiveness and safety in early pregnancy.

What is cannabinoid hyperemesis syndrome in pregnancy?

Though cannabis has antiemetic effect, chronic cannabis user may develop cannabinoid hyperemesis syndrome (CHS) during pregnancy. This syndrome is characterized by cyclic intractable nausea/vomiting and abnormal bathing behaviors. CHS is usually resistant to standard antiemetics and subsides only with cannabis abstinence.

Cannabinoid hyperemesis syndrome (CHS), was first described in chronic cannabis user by Allen et al[28] in 2004. It is characterized by cyclic intractable nausea/vomiting with abdominal pain, and abnormal bathing behaviors (for example showering in hot water for hours each time and multiple times per day). CHS is often resistant to standard antiemetics and subsides only with cannabis abstinence. Hot showers and baths were also reported to be effective in relieving symptoms[29-31].

Obstetricians may be familiar with antiemetic properties of cannabis, but may not be aware of its paradoxical reaction. Hence, in pregnant women who have severe nausea and vomiting which are not relieved by antiemetics, obstetricians should be aware of CHS by inquiring about cannabis use and bathing behaviors.

Should cannabis be used to support pregnant women who have labor pain?

No clinical study has supported the use of cannabis for labor pain. However, in the lay press, many pregnant women had reported their positive experiences from cannabis during their final stage of pregnancy.

Cannabis has been reported to be associated with the improvement of chronic pain in many studies, though with only moderate-quality evidence[19]. Considering labor pain, no evidence in the medical literature supports its uses. However, in the lay press, pregnant women had reported their positive experiences with CBD and THC during the final stage of pregnancy[32,33]. They believed that CBD in conjunction with THC can decrease labor pain and speed up contractions[33]. Some also questioned whether cannabis may replace oxytocin and epidural block or other conventional labor pain medications[33]. The advantage of using cannabis instead of oxytocin is that cannabis has no hyper-stimulation effect[33].

Methods of self-cannabis treatment in final stage of pregnancy include bath bombs, cervical ointments, tinctures, distillate pills, etc.[33].

Is there any adverse outcome in pregnant women who used cannabis?

The results from previous reports are still conflicting. Nevertheless, one meta-analytic study demonstrated a higher rate of low birth weight, neonatal intensive care unit admission and maternal anemia. Until more data are available to support its safety, women should be advised not to use cannabis during pregnancy or while lactating.

With the legalization for medical use of cannabis, it is possible that cannabis use in pregnant women may increase. In animal, there is evidence that THC can cross the placenta although at low level[34]. Hence, obstetricians should know whether cannabis use in pregnancy will cause any adverse fetal and also maternal outcomes.

In human studies, the results of neonatal outcomes from cannabis use in pregnancy are conflicting. Many studies have shown associations between cannabis use and preterm labor[35,36], low birth weight[37,38], neonatal intensive care unit admissions[35], and stillbirth[39], while others have found no impact on birth outcomes[40-42]. However, the meta-analytic study by Gunn et al[43] which included 24 studies, reported that infants exposed to cannabis in utero had higher rate of low birth weight (OR=1.77: 95% CI 1.04 to 3.01; mean difference of birth weight = 109.42 g: 38.72 to 180.12) and neonatal intensive care

unit admission (OR = 2.02: 1.27 to 3.21) compared with infants of the non-users. This meta-analysis also demonstrated that women who used cannabis during pregnancy had an increase rate of anemia (OR 1.36: 95% CI 1.10 to 1.69).

Can cannabis help with dysmenorrhea?

There has been no evidence from clinical study to support the use of cannabis for menstrual pain. However, in the lay press, various forms of cannabis were claimed to reduce or even eliminate the menstrual pain.

People use cannabis for menstrual pain relief for a long time. Queen Victoria was also said to use cannabis for this purpose. However, from the literature review, there is only one clinical study reported about the use of cannabis for menstrual pain[44]. In that study (reported in 1847), the patient received the tincture of the Cannabis indica with unfavorable results[44].

Though there is no formal clinical study support the use of cannabis for menstrual pain or dysmenorrhea; pharmacologically, cannabis should have benefits for menstrual pain because CBD may provide pain relieve while both CBD and THC have muscle relaxant effects that can reduce the spasms associated with menstrual cramps. Moreover, THC will provide anxiolytic effect and euphoria mood[45]. At present, there are lots of cannabis products in many forms such as bath salts, body balm, vaginal cream, vagina supossitory, tincture, eatable cocao, butter, etc[46,47]. Russel[47] reported in 2016 that she had tried 7 cannabis products and found that all helped her severe menstrual cramp, but her favorites were vaginal suppository and the CBD tincture. For vaginal suppository, her whole painful pelvis was suddenly unlocked after insertion around 10-15 minutes. For CBD tincture, which has a 15:1 ratio of CBD to THC, her pain was eliminated around five minutes after she had a couple drops under her tongue.

In some states of America, lawmakers are pushing to add menstrual pain to the list of conditions that justify the medical use of cannabis[46].

Should cannabis be used as antiemetics in gynecologic cancer patients who received chemotherapy?

Both herbal cannabis and synthetic cannabinoids are not recommended as a first-line antiemetic because new standard antiemetics (5-HT3 receptor antagonists, and neurokinin-1-receptor-antagonists) are potent and without any psychotropic effects. However, cannabis may be useful in those cancer patients whose nausea and vomiting cannot be controlled by the new standard antiemetics.

Herbal cannabis has been claimed to have benefit in chemotherapy induced nausea and vomiting (CINV). However, most of the published studies are only observational or uncontrolled study without any randomized controlled trial. Besides, there is still lack of standardization regarding dosing and potency in their uses[48]. Hence, herbal cannabis, at present is not recommended for CINV[49].

On the other hand, synthetic cannabinoids [nabilone (Cesamet- a synthetic analog of THC) and dronabinol (Marinol-synthetic THC)], or whole plant extract (e.g. nabiximols) were tested in lots of controlled clinical trials.

In early 1980s, nabilone was licensed for CINV while dronabinol was also licensed as antiemesis in 1985[50]. Considerable systematics reviews confirmed that these synthetic THC and whole plant extract (e.g. nabiximols) were significantly more effective than placebo and at least as effective as various conventional antiemetics such as prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride[23, 51]. However, most evidences had only moderate quality[49]. From subgroup analysis, patients receiving cannabinoids had better control in those who received moderate emetogenic chemotherapy regimens but had similar efficacy in those who received a low or highly emetogenic chemotherapy regimen[23]. Despite this result, one drawback was the significant more adverse events observed among those who received

cannabinoids[23]. These adverse events included sedation, drowsiness, euphoria, dizziness, dysphoria, depression, hallucinations, paranoia, and hypotension[23].

Since most of these studies were conducted before the emergence of 5-HT3 receptor antagonists and neurokinin-1-receptor-antagonists (NK-1 antagonists), which are the standard anti-emetic agents at present[52]. As of now, there has been no published randomized controlled trial comparing cannabinoids with NK-1 antagonists. Only one published randomized controlled trial, that compared dronabinol alone and in combination with ondansetron versus ondansetron alone in patients receiving moderately to highly emetogenic chemotherapy, was available[53]. This study concluded that dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone.

For the reason that 5-HT3 receptor antagonists (such as ondansetron, granisetron, dolasetron, etc.) are potent and do not have psychotropic effects[52], synthetic cannabinoids are not recommended as first-line antiemetics. Nonetheless, they may be useful in some cancer patients whose nausea and vomiting can not be controlled by 5-HT3 receptor antagonists or by NK-1 antagonists.

Can cannabis cure cancer?

Lots of evidences from preclinical studies showed that cannabinoids had antitumor effect. Clinically, most case reports were only in lay press. To date, there is not enough data to confirm their effectiveness as therapeutic agents for cancer.

Cannabinoids are well-known of their palliative effects on some cancer-associated symptoms such as cancer-related pain, chemotherapy-induced nausea and vomiting, and anorexia. Moreover; in preclinical studies, lots of evidences show that these molecules may have antitumor effects. The anticancer mechanisms of cannabinoids included antiproliferative, anti-metastatic, antiangiogenic, and proapoptotic effects[54,55]. Adding, cannabis extracts with a variety of chemotherapy in vitro and in animals models demonstrated synergism in reducing tumor cells[54]. Despite these evidences, some studies reported discordant results that antitumor effect of cannabinoids was demonstrated only with higher drug doses whereas their lower doses would stimulate cancer proliferation[54].

Besides these preclinical studies, most of the clinical reports which claimed that cannabis can treat human cancer were in the lay press, especially the internet and mostly with anonymous authored. Here are a few stories of those who believed that they had advantage from cannabis as cancer treatment.

Sharon Kelly, a 54- year-old Australian woman had posted on youtube that she had successfully treated her stage IV lung cancer with lymph node metastasis by using cannabis oil. She had cancer free after only 7 months on cannabis.

Rick Simpson had successfully treated his basal cell carcinoma by topically applying concentrated cannabis oil which he named it “Rick Simpson oil”[56]. He had written a book of 129 pages entitled “Phoenix Tears Rick Simpson Oil Nature’s Answer For Cancer”[56]. In this book he described how to make the oil, and conditions that could be improved or cured by using his oil. For skin cancer, he suggested the oil application to the cancer area and cover it with a bandage, then reapply fresh oil and a new bandage every three or four days and the cancer should soon disappear (mostly within 3 weeks)[56].

In Thailand, Buntoon Niyamapa, had made cannabis oil according to Simpson technique and reported that it helped his sister to remain cancer-free after treatment of uterine cancer by surgery and radiotherapy. He was then well known for his oil, lots of cancer patients came to see him for cannabis oil. He claimed that his oil can prolong life in cancer patients and can cure in some cases. Although some patients were not cured, they were less suffering from their cancer related symptoms[57].

Since most of the case reports were in the lay press. At present, there is not enough data to confirm their effectiveness as therapeutic agents.

Is cannabis addictive?

Tetrahydrocannabinol has the potential

additive effect but not in the same extent as other drugs whereas cannabidiol has no any abuse or dependence potential.

Most of the evidences suggest that THC has the potential additive effect but not in the same extent as other drugs such as opiate, met-amphetamine, cocaine, etc. In animal model, THC can induce animal to self-administer the drug, which suggested that it has additive potential[58]. Freeman and Winstock[59] reported that only a minority of cannabis users become addicted, while Hasin et al[60] reported that 30 % of those who used cannabis may have some degree of cannabis-related disorders.

Flórez-Salamanca et al[61] and Lopez-Quintero, et al[62], reported that lifetime cumulative probability of individuals with cannabis abuse that would evolute to dependence at some point in their lives were 8.9-9.4% which were lower than 15.6-20.9 % from cocaine, 22.7-26.6% from alcohol and 67.5% from tobacco.

Factors associated with vulnerability of cannabis addiction included male gender, young age, concurrent tobacco use, frequent (especially daily) and high-potency cannabis use[59,63].

CBD counter act THC indirectly by antagonist at CB1, CB2 and other orphan receptors. In humans, CBD exhibits no effect indicative of any abuse or dependence potential. People who smoked cannabis containing high levels of CBD were less prone to have their attention captured by cannabis-related stimuli than were those smoking cannabis with low CBD content. Several countries have modified their national controls to accommodate CBD as a medicinal product.

Are there any withdrawal symptoms in cannabis users?

The cannabis withdrawal symptoms such as irritability, sleep difficulty, depressed mood, decrease appetite may appear within 1-2 days after cessation in those with prolonged and heavy use. These symptoms are usually mild and can resolve within 1-2 weeks.

For cannabis user, withdrawal symptoms seldom represent a problem since they only ever occur in heavy users after abrupt cessation[63]. In heavy or prolonged cannabis use, these symptoms appear within 1-2 days after discontinuation and peak after 2-6 days[64]. Most symptoms are mild and mostly resolve within 1-2 weeks. Cannabis withdrawal symptoms include irritability, anxiety, muscle pain, chills, sleep difficulty, insomnia, nightmares, headache, decreased appetite, depressed mood, etc[64,65]. Unfortunately, antidepressants, anxiolytics, noradrenaline-reuptake inhibitors, and anticonvulsants have not been approved to alleviate cannabis withdrawal symptoms[10].

Is cannabis safe for medical use?

Although cannabis has lots of adverse events, most of these adverse events in the medical use are not serious. However, long-term treatment in children and adolescents should be cautious because of the much higher risk of cognitive impairments in these age groups.

No acute death has been attributed solely from cannabis consumption or treatment with cannabinoids[63]. However, there are lots of adverse effects reported in cannabis users. Most of these adverse effects were reported from studies of recreational users of cannabis. These adverse effects include impairment of memory, reductions in psychomotor and cognitive performance, euphoria, disorientation, drowsiness, confusion, loss of balance, and anxiety. Other frequent physical effects of cannabinoids are tiredness, dizziness, tachycardia, orthostatic hypotension, dry mouth, nausea, vomiting, fatigue, somnolence, reduced lacrimation, muscle relaxation, increased appetite, myocardial infarction, stroke, and transient ischemic attack[19,24,63]. Heavy or long-term use of cannabis is associated with chronic bronchitis and chronic psychosis-related health disorders, including schizophrenia and depression[24]. Myocardial infarction, stroke, and transient ischemic attack have also been associated with cannabis use[24].

Concerning the safety of cannabis in medical use, Wang et al[66] had performed a systematic review of medical cannabinoids from 31 published studies. They reported that 96.6% of all reported adverse

effects were determined by authors to be non-serious. The most common non-serious adverse event was dizziness (15.5%) whereas the most common serious adverse effects included relapsing multiple sclerosis (12.8%), vomiting (9.8%), and urinary tract infections (9.1%). However, the rate of serious adverse event was not significantly different from the control.

While medical cannabis seems to be safe, long-term treatment in children and adolescents should be cautious because the risk of cognitive impairments is much higher in these age groups[63].

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Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Adverse Outcomes of Pregnancy with Abnormal Weight Gain at Phramongkutklao Hospital

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ABSTRACT

Objectives: To determine adverse maternal and neonatal outcomes of pregnant women who did not reach optimal gestational weight gain (GWG).

Materials and Methods: Medical records of 2,103 term singleton delivery at Phramongkutklao Hospital during 1 January 2013 – 31 December 2015 were retrospectively reviewed. According to Institute of Medicine (IOM) 2009 guideline, the pregnant women were categorized into 3 groups (701 subjects in each group); less than optimal GWG, optimal GWG and excessive GWG corresponding to their pre-pregnancy body mass index (BMI) classified by World Health Organization (WHO) for Asian population. Adverse pregnancy outcomes were compared between groups.

Results: Excessive GWG was significantly associated with gestational hypertension ($p < 0.001$), preeclampsia ($p = 0.003$), cesarean section ($p < 0.001$), large for gestational age ($p < 0.001$), macrosomia ($p = 0.005$) and hyperbilirubinemia ($p < 0.001$). Less GWG was significantly related to intrauterine growth restriction ($p < 0.001$), small for gestational age ($p < 0.001$) and low birth weight ($p < 0.001$) but was associated with significant good pregnancy outcomes in terms of successful vaginal delivery ($p < 0.001$), first degree perineal injury ($p < 0.001$). Multiple logistic regression analysis adjusted for maternal age, gestational age, and pre-pregnancy BMI further confirmed the aforementioned associations.

Conclusion: Women with abnormal gestational weight gain are at risk for adverse maternal and neonatal outcomes.

Keywords: adverse outcomes of pregnancy, gestational weight gain, pre-pregnancy BMI

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ผลการตั้งครรภ์อันไม่พึงประสงค์ในหญิงตั้งครรภ์ที่น้ำหนักตัวระหว่างการตั้งครรภ์เพิ่มขึ้นผิดปกติ ในโรงพยาบาลพระมงกุฎเกล้า

ณิชชาณัท ชัยพงศ์พันธุ์, พีระพรรณ พันธุ์ภักดีคุณ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลการตั้งครรภ์อันไม่พึงประสงค์ ทั้งด้านมารดาและทารก ในหญิงตั้งครรภ์ที่มีน้ำหนักตัวเพิ่มขึ้นผิดปกติระหว่างการตั้งครรภ์*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลัง โดยทบทวนเวชระเบียนของหญิงตั้งครรภ์ที่มาฝากครรภ์และคลอดที่โรงพยาบาลพระมงกุฎเกล้า ในระหว่างวันที่ 1 มกราคม 2556 ถึงวันที่ 31 ธันวาคม 2558 จำนวน 2,103 คน แบ่งหญิงตั้งครรภ์ออกเป็น 3 กลุ่ม (กลุ่มละ 701 คน) ได้แก่ หญิงตั้งครรภ์ที่น้ำหนักตัวเพิ่มขึ้นน้อยกว่าเกณฑ์ หญิงตั้งครรภ์ที่น้ำหนักตัวเพิ่มขึ้นตามเกณฑ์ และหญิงตั้งครรภ์ที่น้ำหนักตัวเพิ่มขึ้นมากกว่าเกณฑ์ โดยอ้างอิงน้ำหนักตัวที่เพิ่มขึ้นอย่างเหมาะสมในแต่ละช่วงดัชนีมวลกายตามคำแนะนำของ Institute of Medicine (IOM) 2009 และจัดกลุ่มดัชนีมวลกายสำหรับประชากรเอเชีย ตามคำแนะนำขององค์การอนามัยโลก (WHO) เปรียบเทียบผลการตั้งครรภ์อันไม่พึงประสงค์ทั้งทางด้านมารดาและทารกในหญิงตั้งครรภ์ทั้งสามกลุ่ม*

ผลการศึกษา: *หญิงตั้งครรภ์ที่น้ำหนักตัวเพิ่มขึ้นมากกว่าเกณฑ์ มีความเสี่ยงในการเกิดภาวะความดันโลหิตสูงระหว่างตั้งครรภ์ ($p < 0.001$), ครรภ์เป็นพิษ ($p = 0.003$), อัตราการผ่าท้องทำคลอด ($p < 0.001$), คลอดทารกตัวโตกว่าอายุครรภ์ ($p < 0.001$), ทารกตัวโต ($p = 0.005$) และ ภาวะระดับบิลิรูบินสูงในเลือด ($p < 0.001$) เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ ในกลุ่มหญิงตั้งครรภ์ที่น้ำหนักตัวเพิ่มขึ้นน้อยกว่าเกณฑ์ พบว่ามีความเสี่ยงในการเกิดภาวะทารกโตช้าในครรภ์ ($p < 0.001$), ทารกตัวเล็กกว่าอายุครรภ์ ($p < 0.001$) และทารกน้ำหนักตัวน้อย ($p < 0.001$) เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ แต่พบว่ามีผลดีต่อการตั้งครรภ์ คือ มีการคลอดทางช่องคลอดเพิ่มขึ้น ($p < 0.001$) และมีแผลฉีกขาดบริเวณฝีเย็บระดับที่ 1 ($p < 0.001$) เมื่อวิเคราะห์โดยการถดถอยพหุโลจิสติกส์ (multiple logistic regression) โดยตัดปัจจัยเรื่องอายุของหญิงตั้งครรภ์ อายุครรภ์ และดัชนีมวลกายก่อนการตั้งครรภ์ออก ยังคงพบความสัมพันธ์ดังกล่าว*

สรุป: *หญิงตั้งครรภ์ที่มีน้ำหนักตัวเพิ่มขึ้นผิดปกติระหว่างตั้งครรภ์ มีความเสี่ยงในการเกิดผลการตั้งครรภ์อันไม่พึงประสงค์ทั้งทางด้านมารดาและทารก*

คำสำคัญ: *ผลการตั้งครรภ์อันไม่พึงประสงค์ น้ำหนักตัวที่เพิ่มขึ้นระหว่างการตั้งครรภ์ ดัชนีมวลกายก่อนการตั้งครรภ์*

Introduction

Obesity and overweight are the important problems worldwide. During the past 20 years, the incidence of obesity and overweight has increased dramatically to 40% in Europe and 44% in the United States. In 2010, the incidence of obese and overweight in Thailand were 17.1% and 23.8 %, respectively[1]. World Health Organization (WHO) has classified the body mass index (BMI) for Asian population into 4 levels: underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5-22.9 kg/m^2), overweight (BMI 23-24.9 kg/m^2) and obese (BMI > 25 kg/m^2)[2].

The Institute of Medicine (IOM) 2009 develops guideline for optimal weight gain during pregnancy. Total weight gain throughout pregnancy should be 12.5-18 kg, 11.5-16 kg, 7-15 kg, and 5-9 kg for those whose prepregnancy BMI are classified as underweight, normal, overweight, and obesity, respectively[3]. Obese pregnant women increase risk for adverse maternal and neonatal outcomes such as gestational diabetic mellitus (GDM)[4-6], gestational hypertension (GHT), preeclampsia[5,6], increased risk for cesarean section[6,7], postpartum hemorrhage (PPH), uterine atony, unexplained stillbirth[8,9], shoulder dystocia, obesity in childhood[6]. Underweight pregnant women has increased risk for preterm birth[10,11], small for gestational age (SGA)[12]. In addition, excessive weight gain during pregnancy has increased risk for GHT, PPH, cesarean section and macrosomia. Inversely, pregnant women with less than optimal weight gain have increased risk for SGA.

The studies about the relationship between weight gain during pregnancy and adverse maternal and neonatal outcomes mostly use pre-pregnancy BMI of European and American population which may not be suitable to imply the results for Thai population. Thereby, this study aimed to explore adverse maternal and neonatal outcomes of pregnant women who had not reached optimal weight gain at Phramongkutklao Hospital by using World Health Organization (WHO) BMI classification for Asian population.

Materials and Methods

This retrospective study was approved by the Ethic Committee of the Institutional Review Board of the Royal Thai Army Medicine Department. Medical records of all pregnant women with term singleton and delivered at Phramongkutklao Hospital during 1 January 2013 – 31 December 2015 were reviewed. Pregnant women with pre-gestational diabetic mellitus, chronic hypertension (CHT), systemic lupus erythematosus (SLE), antiphospholipid syndrome, missing data of the pre-pregnancy body weight or height, first antenatal visit beyond gestational age (GA) 20 weeks, preterm birth, and those with fetal anomaly were excluded[13,14].

Pre-pregnancy BMI was calculated by dividing maternal pre-pregnancy body weight (kilogram) by square of height (meter^2) which was reported by pregnant women at first antenatal visit. Gestational weight gain was the difference between maternal body weight at admission date in labor room and pre-pregnancy body weight. All pregnant women were allocated by pre-pregnancy BMI into four groups according to the WHO classification. Then, each group would be further divided into three groups according to the gestational weight gain (GWG) recommended by the IOM 2009 guideline; less than optimal weight gain, optimal weight gain and excessive than optimal weight gain.

Pregnant women's demographic data including age, parity, GA at delivery, underlying disease were collected.

Adverse maternal outcomes including GHT, preeclampsia, eclampsia, GDM, premature rupture of membranes (PROM), PPH (estimated blood loss > 500 ml for vaginal delivery or > 1,000 ml for cesarean section)[15], mode of delivery (operative vaginal delivery or cesarean section) and degree of perineal laceration (3rd to 4th degree tear) were recorded. GHT was diagnosed in women whose blood pressures reach 140/90 mmHg or greater for the first time after midpregnancy but in whom proteinuria was not identified. Preeclampsia was diagnosed when blood pressure reached 140/90 mmHg or greater plus proteinuria for the first time after midpregnancy, and

eclampsia was diagnosed if seizure was present (15). GDM was diagnosed by 100-gram oral glucose tolerance test (100g OGTT); fasting blood sugar, one, two and three hours blood glucose were examined after administration of 100 g oral glucose. If at least two of four values were abnormal, GDM was diagnosed (≥ 95, ≥ 180, ≥ 155, ≥ 140 mg/dl, respectively)[16-18]. First-degree laceration was defined as an involvement of the fourchette, perineal skin, periurethral lacerations and vaginal mucous membrane but not the underlying fascia and muscle. Second-degree laceration was defined as an involvement of the fascia and muscles of the perineal body but not the anal sphincter. Third-degree and fourth-degree lacerations were defined when the external anal sphincter and rectal mucosa were disrupted, respectively[15].

Adverse neonatal outcomes which consisted of symmetrical intrauterine growth restriction (IUGR) (estimated fetal weight less than 10th percentile for their gestational age, head-to-abdomen circumference ratio were proportionately small)[19], asymmetrical IUGR (estimated fetal weight less than 10th percentile for their gestational age, head-to-abdomen circumference ratio were disproportionately lagging abdominal growth)[19], stillbirth, large for gestational age (LGA)(birth weight > 90th percentile for gestational age at birth)[15]. SGA (birth weight < 10th percentile for gestational age at birth)[15], low birth weight (LBW) (birth weight < 2,500 grams)[15], birth asphyxia (Apgar score less than 7 at 5 min after delivery)[15], shoulder dystocia (head-to-body delivery time > 60 seconds)[15], neonatal hypoglycemia (blood sugar < 45 mg/dl at 12 hours postpartum)[15], fetal macrosomia (birth weight > 4000 grams)[15], hyperbilirubinemia (treated with phototherapy)[20], respiratory distress syndrome (RDS) (respiratory insufficiency with hypoxemia and compensatory tachypnea)[15], neonatal admission to neonatal intensive care unit (NICU) within 48 hours postpartum, neonatal sepsis and neonatal death were recorded.

Sample size calculation in this study was based on Enomoto K. et al study[21] that reported 4.79 percent of pregnancy induced hypertension among optimal weight gain pregnant women. To get power of 80 percent and alpha error of 0.05, we needed 701 participants in each study group. Non-probability sampling of medical records was done retrospectively until 701 participants in each gestational weight gain groups were obtained.

The statistical analysis was performed by using SPSS statistical software version 17 (SPSS Inc, Chicago, IL, USA). One-way analysis of variance (ANOVA) was used to compare continuous data and expressed as mean ± standard deviation. The Chi-square test or Fisher's exact test was used for the comparison of categorical data. Multiple logistic regression was used for controlling confounding factors including maternal age, gestational age and pre-pregnancy BMI and expressed as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). The statistical significance was considered when p value was less than 0.05.

Results

This study included 2,103 pregnancies; with equal number of 701 subjects in each gestational weight gain group. Table 1 shows maternal characteristics. The mean age among women with less than optimal weight gain was significantly lower than those with optimal weight gain and excess than optimal weight gain (28.87 ± 6.09, 29.36 ± 5.61, 29.95 ± 5.42; p=0.002). Nearly half of our populations were categorized according to their prepregnancy BMI as normal weight (n = 1,024; 48.7%), while the remaining was underweight (n = 471; 22.4%), overweight (n = 291; 13.8%) and obese (n = 317; 15.1%). The mean of pre-pregnancy BMI was also significantly higher in pregnant women with excess than optimal weight gain (23.22 ± 4.18 kg/m^2) while those with less than optimal weight gain and optimal weight gain had similar prepregnancy BMI (20.64 ± 3.75 and 20.86 ± 3.53).

The adverse maternal outcomes are demonstrated in Table 2. Pregnant women who gained excess weight were significantly complicated with GHT (7.7%; p < 0.001), preeclampsia (3.7%; p =

0.003), higher cesarean section rate (46.4%; p < 0.001) mostly due to cephalopelvic disproportion (CPD) (52.0%). In contrast, less than optimal weight gain women had significantly higher successful rate for vaginal delivery (73.3%; p < 0.001), with higher rate for first degree perineal injury (p < 0.001).

Table 1. Maternal demographic characteristics (N=2,103).

Characteristics	Less than optimal (n=701)		Optimal (n=701)		Excess than optimal (n=701)		p value
	n	%	n	%	n	%	
Age (years)							0.023
< 20	40	5.7	33	4.7	20	2.9	
20-35	383	54.6	364	51.9	356	50.8	
> 35	278	39.7	304	43.4	325	46.4	
Mean±S.D.	28.87 ± 6.09^{A}		29.36 ± 5.61^{AB}		29.95±5.42^{B}		0.002$^{\#}$
Prepregnancy-BMI							< 0.001
Underweight	211	30.1	188	26.8	72	10.3	
Normal weight	378	53.9	367	52.4	279	39.8	
Overweight	54	7.7	87	12.4	150	21.4	
Obese	58	8.3	59	8.4	200	28.5	
Mean±S.D.	20.64 ± 3.75^{A}		20.86 ± 3.53^{A}		23.22 ± 4.18^{B}		< 0.001$^{\#}$
Parity							0.337
Nulliparous	379	54.1	353	50.4	374	53.4	
Multiparous	322	45.9	348	49.6	327	46.6	
GA at delivery (weeks)							
Mean±S.D.	38.32 ± 0.93^{A}		38.47 ± 1.00^{B}		38.60 ± 1.07^{C}		< 0.001$^{\#}$
Underlying disease							
Asthma	4	0.6	1	0.1	2	0.3	0.367
Thalassemia trait	175	25.0	201	28.7	184	26.2	0.280
Thyroid disease	16	2.3	14	2.0	17	2.4	0.859
Others	31	4.4	44	6.3	39	5.6	0.302

$^{A, B, C}$ = Difference characters mean significant difference between groups in multiple comparisons
p value from Chi-Square test, $^{\#}$ = p value from One-way ANOVA,
prepregnancy BMI = prepregnancy body mass index (WHO classification)

The adverse neonatal outcomes are demonstrated in Table 3. The mean birth weight of women with less than optimal, optimal and excess than optimal weight gain were considerably different (2,948.60 ± 377.47, 3,078.48 ± 371.26 and 3,229.02 ± 433.98; p < 0.001). Pregnant women who had excessive gestational weight gain were significantly complicated with LGA (p < 0.001), macrosomia (p = 0.005) and hyperbilirubinemia (p < 0.001). In contrast, pregnant women with less than optimal weight gain were significantly affected with IUGR (p < 0.001), SGA (p < 0.001) and LBW (p < 0.001).

Table 2. Adverse maternal outcomes (N = 2,103).

	Less than optimal (n=701)		Optimal (n= 701)		Excess than optimal (n = 701)		p value
	n	%	n	%	n	%	
Hypertension in pregnancy	21	3.0	31	4.4	81	11.6	< 0.001
Gestational hypertension	14	2.0	16	2.3	54	7.7	< 0.001
Preeclampsia	7	1.0	15	2.1	26	3.7	0.003
Eclampsia	0	0	0	0	1	0.1	0.368
Gestational diabetes mellitus	81	11.6	92	13.1	104	14.8	0.192
Insulin							0.141
Insulin used	10	12.3	10	10.9	21	20.2	
Non-insulin used	71	87.7	82	89.1	83	79.8	
Premature rupture of membranes	11	1.6	10	1.4	19	2.7	0.156
Postpartum hemorrhage	25	3.6	21	3.0	29	4.1	0.515
Route of delivery							
Spontaneous vertex	514	73.3	471	67.2	364	51.9	< 0.001
Forceps extraction	3	0.4	5	0.7	9	1.3	0.190
Vacuum extraction	1	0.1	1	0.1	2	0.3	0.778
Breech assisting	0	0	1	0.1	1	0.1	0.606
Cesarean section	183	26.1	223	31.8	325	46.4	< 0.001
Cesarean section (indication)							
Cephalopelvic disproportion	73	39.9	96	43.0	169	52.0	
Breech presentation	14	7.7	22	9.9	22	6.8	
Unfavorable cervix	2	1.1	6	2.7	10	3.1	
Failed induction	9	4.9	5	2.2	13	4.0	
Placenta previa	4	2.2	2	0.9	8	2.5	
Fetal distress	8	4.4	16	7.2	16	4.9	
Prolapsed cord					1	0.3	
Oblique lie					1	0.3	
Transverse lie					2	0.6	
Perineal injury[#]	505	97.5	465	97.3	365	97.1	< 0.930
First degree tear	48	9.3	24	5.0	11	2.9	< 0.001
Second degree tear	444	85.7	399	83.5	319	84.8	0.615
Third degree tear	13	2.5	38	7.9	31	8.2	< 0.001
Fourth degree tear	0	0	4	0.8	4	1.1	0.034[F]

p value from Chi-Square test, [F] = p value from Fisher's exact test

[#] Percentage among pregnant women who delivered vaginally

Table 3. Adverse neonatal outcomes (N = 2,103).

	Less than optimal (n = 701)		Optimal (n = 701)		Excess than optimal (n = 701)		p value
	n	%	n	%	n	%	
IUGR	26	3.7	14	2.0	4	0.6	< 0.001
IUGR type							0.381
Symmetrical IUGR	15	57.7	11	78.6	3	75.0	
Asymmetrical IUGR	11	42.3	3	21.4	1	25.0	
Stillborn	2	0.3	1	0.1	0	0	0.367
Birth weight Mean ± S.D.	2,948.60 ± 377.47A		3,078.48 ± 371.26B		3,229.02 ± 433.98C		< 0.001#
AGA	610	87.0	645	92.0	582	83.0	< 0.001
SGA	61	8.7	21	3.0	17	2.4	< 0.001
LGA	30	4.3	35	5.0	102	14.6	< 0.001
Macrosomia	2	0.3	3	0.4	12	1.7	0.005
Low birth weight	65	9.3	31	4.4	27	3.9	< 0.001
Apgar score at 1 min (<7)	24	3.4	23	3.3	36	5.1	0.140
Apgar score at 5 min (<7)	3	0.4	2	0.3	3	0.4	0.882
Shoulder dystocia	0	0	0	0	0	0	
Neonatal hypoglycemia	5	0.7	9	1.3	9	1.3	0.495
Hyperbilirubinemia	122	17.4	160	22.8	210	30.0	< 0.001
RDS	5	0.7	5	0.7	8	1.1	0.604
Admission to NICU	2	0.3	2	0.3	3	0.4	1.000F
Neonatal sepsis	13	1.9	12	1.7	13	1.9	0.974
Neonatal death	1	0.1	0	0	0	0	1.000F

A, B, C = Difference characters mean significant difference between groups in multiple comparisons
p value from Chi-Square test, F = p value from Fisher's exact Test, # = p value from One-way ANOVA
AGA; appropriate for gestational age, IUGR; intrauterine growth restriction, LGA; large for gestational age, NICU; neonatal intensive care unit, RDS; respiratory distress syndrome, SGA; small for gestational age

Multiple logistic regression analysis was utilized to estimate the association between abnormal weight gain during pregnancy and the risk of adverse outcomes while controlling potentially confounding variables including maternal age, gestational age and pre-pregnancy BMI as demonstrated in Table 4. Women with excessive GWG significantly increased risk for GHT (adjusted odds ratios (aOR) 3.14; 95% CI 1.73-5.68) and cesarean section (aOR 1.67; 95%CI 1.32-2.1). Whereas, vaginal delivery was highly related to those with less than optimal weight gain (aOR 1.33; 95%CI 1.05-1.69).

Table 5 shows the association between pre-pregnancy BMI and adverse maternal and neonatal outcomes. Underweight women had significantly higher successful rate for vaginal delivery (71.1%; p < 0.001). Moreover, underweight women were significantly higher risk for IUGR (4.5%; p < 0.001) and SGA (9.1%; p < 0.001). Normal weight women were significantly higher appropriate gestational age

(AGA) 90.4% (p < 0.001). Obese women were significantly affected with GHT (9.1%), delivered by cesarean section (50.8%) and delivered LGA newborns (15.8%).

Table 4. Multiple logistic regression analysis of pregnancy outcomes.

	Less than optimal		p value	Excess than optimal		p value
	Adjusted OR	95%CI		Adjusted OR	95%CI	
Hypertension in pregnancy	0.65	(0.37-1.14)	0.130	2.67	(1.70-4.20)	< 0.001
Gestational hypertension	0.83	(0.40-1.72)	0.611	3.14	(1.73-5.68)	< 0.001
Preeclampsia	0.46	(0.19-1.14)	0.093	1.86	(0.95-3.66)	0.072
Spontaneous vertex delivery	1.33	(1.05-1.69)	0.017	0.58	(0.46-0.73)	< 0.001
Cesarean section	0.76	(0.60-0.97)	0.025	1.67	(1.32-2.10)	< 0.001
Perineal injury						
First degree tear	1.90	(1.14-3.15)	0.014	0.54	(0.25-1.18)	0.123
Third degree tear	0.31	(0.16-0.59)	< 0.001	1.03	(0.61-1.74)	0.908
AGA	0.58	(0.41-0.82)	0.002	0.47	(0.33-0.67)	< 0.001
SGA	2.93	(1.76-4.87)	< 0.001	1.07	(0.54-2.10)	0.851
LGA	0.93	(0.56-1.54)	0.766	2.61	(1.72-3.96)	< 0.001
Macrosomia	0.74	(0.12-4.50)	0.745	3.25	(0.89-11.93)	0.075
Low birth weight	1.97	(1.26-3.09)	0.003	1.21	(0.69-2.11)	0.506
IUGR	1.60	(0.82-3.12)	0.170	0.41	(0.13-1.32)	0.133
Hyperbilirubinemia	0.70	(0.54-0.92)	0.009	1.41	(1.10-1.82)	0.007

Multiple logistic regression models adjusted for maternal age, gestational age, pre-pregnancy BMI
AGA; appropriate for gestational age, IUGR; intrauterine growth restriction, LGA; large for gestational age, SGA; small for gestational age

Discussion

Our study suggested that both pre-pregnancy BMI and GWG were associated with adverse maternal and neonatal outcomes. We found that pregnant women who had normal weight before pregnancy or pregnant women who had optimal weight gain had better outcomes.

Considering GWG, our data showed that less than optimal GWG had higher risk for IUGR, SGA and LBW and also higher successful rate for vaginal delivery and first degree perineal injury. Excess than optimal weight gain increased maternal risk for GHT, preeclampsia and cesarean section due to CPD and also increased neonatal risk for LGA, macrosomia and hyperbilirubinemia which were similar to previous studies[21-28]. The mechanism of hyperbilirubinemia is unclear, may be associated with fetal hyperinsulinemia which increases glycolysis and erythropoiesis[26]. Our data highlighted the importance of adherence to recommended GWG to optimize pregnancy outcomes.

We also found 2 stillbirths with unexplained cause. Both pregnant women were healthy without any poor obstetric and medical condition during antenatal care and no fetal and placental abnormality were found. One was underweight and gained less than optimal GWG but we did not find association between pre-pregnancy BMI, GWG and stillbirth which was consistent to Chibber R, et al study[29].

Table 5. Adverse maternal and neonatal outcomes according to pre-pregnancy BMI.

	Pre-pregnancy-BMI								p value
	Underweight (n = 471)		Normal weight (n = 1024)		Overweight (n = 291)		Obese (n = 317)		
Hypertension in pregnancy	22	4.7	52	5.1	17	5.8	42	13.2	<0.001
Gestational hypertension	11	2.3	34	3.3	10	3.4	29	9.1	<0.001
Preeclampsia	11	2.3	17	1.7	7	2.4	13	4.1	0.072
Spontaneous vertex delivery	335	71.1	673	65.7	187	64.3	154	48.6	<0.001
Cesarean section	132	28.0	337	32.9	101	34.7	161	50.8	<0.001
Perineal injury#	333	98.2	669	97.4	179	94.2	154	98.7	0.026
First degree tear	19	5.6	41	6.0	14	7.4	9	5.8	0.866
Second degree tear	291	85.8	581	84.6	156	82.1	134	85.9	0.680
Third degree tear	20	5.9	44	6.4	7	3.7	11	7.1	0.508
Fourth degree tear	3	0.9	3	0.4	2	1.1	0	0.0	0.436
AGA	410	87.0	926	90.4	242	83.2	259	81.7	< 0.001
SGA	43	9.1	39	3.8	9	3.1	8	2.5	< 0.001
LGA	18	3.8	59	5.8	40	13.7	50	15.8	< 0.001
Macrosomia	0	0.0	7	0.7	5	1.7	5	1.6	0.010 F
Low birth weight	45	9.6	51	5.0	13	4.5	14	4.4	0.002
IUGR	21	4.5	19	1.9	2	0.7	2	0.6	< 0.001
Hyperbilirubinemia	93	19.7	233	22.8	82	28.2	84	26.5	0.027

p-value from Chi-Square test, F = p-value from Fisher's exact test
Percentage among pregnant women who delivered vaginally
AGA; appropriate for gestational age, IUGR; intrauterine growth restriction, LGA; large for gestational age, SGA; small for gestational age

According to pre-pregnancy BMI, underweight women had higher risk for IUGR and SGA which were similar to previous studies[21,24,30-31]. In addition, underweight women had higher successful rate for vaginal delivery. In contrast, obese women were at risks for GHT, LGA and increased rate for cesarean section which were consistent with previous studies[21-25, 30-31].

Enomoto K, et al[21] reported that higher pre-pregnancy BMI increased risk for gestational diabetes mellitus but our study failed to find this relationship. We found that higher GWG had higher GDM and higher rate for insulin use but it was not statistically significant.

Multiple logistic regression models was used to adjust for maternal age, gestational age and pre-pregnancy BMI. We found that less than optimal GWG had increased risk of SGA (aOR 2.93; 95%CI: 1.76-4.87) and LBW (aOR 1.97; 95%CI: 1.26-3.09) which were similar to previous studies[21-25, 30-31]. They were more likely to deliver vaginally with first degree tear (aOR 1.90; 95%CI: 1.14-3.15) but less third degree tear (aOR 0.31; 95%CI: 0.16-0.59). In contrast, excessive GWG increased risk for GHT, cesarean section rate, LGA and hyperbilirubinemia. These findings supported that GWG was an independent factor for various pregnancy outcomes.

The findings generated from previous studies are largely based on IOM 2009 GWG guidelines for pre-pregnancy BMI ranges among western populations.

We, instead, classified pre-pregnancy BMI according to WHO classification for Asian population and defined appropriate weight gain for each group by using IOM 2009 guideline since there is currently no recommendation for Asian pregnant women. Our data suggested that adverse maternal and neonatal outcomes were found more among overweight and obese women, which were similar to previous studies[21-25, 30-31]. According to IOM 2009 classification, these groups would be defined as normal BMI and overweight, with the less recommended weight gain. In addition, balancing the risks of fetal growth, obstetrics complications and maternal weight retention is essential. Therefore, IOM 2009 GWG guidelines should be used cautiously in Asian people.

As we found that pregnant women with normal BMI had better outcome, thus, preconceptive counseling for nutrition control and exercise to reach in normal weight may improve pregnancy outcomes. During antenatal care, all pregnant women should be educated of the importance of maintaining their gestational weight gain within a normal range corresponding to their pre-pregnancy BMI. If they have excessive weight gain, increased physical activity and nutrition control by nutritionist may be considered to improve maternal and neonatal outcomes[32].

The strength of our study was the large and equal proportion of subjects in each gestational weight gain group which made the data analysis more reliable.

This study has several limitations that need to be addressed. Firstly, missing data was found in this retrospective study. Secondly, the prepregnancy weight was self-reported, which was abstracted from medical record and subjected to recall error. Finally, there was the limited sample size when assessing the association between GWG and rare pregnancy complications such as shoulder dystocia, stillbirths.

Conclusion

In conclusion, women with abnormal gestational weight gain are at risk for adverse maternal and neonatal outcomes.

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Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Effects of Gestational Weight Gain on Pregnancy Outcomes According to Siriraj Recommendations in Thai Obese Women

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ABSTRACT

Objectives: To evaluate the effect of gestational weight gain on maternal and fetal outcomes according to Siriraj recommendations in Thai obese women.

Materials and Methods: This was a retrospective cohort study of obese Thai women with term-singleton pregnancy. We used The Regional Office for Western Pacific Region of WHO (WPRO) BMI criteria for Asians to define obesity. Data was collected from 1 January 2014 to 31 December 2015. Three hundred and eighty patients were included into this study, 235 patients were in obese class I (BMI 25-29.9 kg/m^2) and 145 patients were in obese class II (BMI >30 kg/m^2). Statistical analyses of adverse maternal and neonatal outcomes between excessive gestational weight gain (GWG) and normal GWG, based on Siriraj recommendations, were assessed.

Results: When compare with normal GWG group, excessive GWG in obese class I and obese class II had greater risk of adverse neonatal outcomes including large for gestational age (LGA), macrosomia and higher birth weight, with statistical significance. Excessive GWG in obese class I and obese class II also had statistically-significant higher risk of adverse maternal outcomes, including severe preeclampsia, postpartum hemorrhage (PPH), cephalopelvic disproportion (CPD) and increased rate of cesarean delivery.

Conclusion: Obese Thai women with term-singleton pregnancy should have GWG according to Siriraj recommendations. Excessive GWG women were associated with increased risk of LGA, macrosomia and higher birth weight. Adverse maternal outcomes were also greater including preeclampsia, PPH, CPD and increased rate of cesarean section.

Keywords: gestational weight gain, obesity, pregnancy outcomes, Siriraj recommendations

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ผลของน้ำหนักที่เพิ่มขึ้นระหว่างตั้งครรภ์ตามคำแนะนำของโรงพยาบาลศิริราชต่อผลลัพธ์ของการตั้งครรภ์ในหญิงไทยที่มีภาวะอ้วน

มารีนา บินระหีม, ศิชฌุพงศ์ หนูทอง, วรางคณา โกละกะ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของน้ำหนักที่เพิ่มขึ้นระหว่างตั้งครรภ์ตามคำแนะนำของโรงพยาบาลศิริราชต่อผลลัพธ์ของการตั้งครรภ์ในหญิงไทยที่ภาวะอ้วน*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงวิเคราะห์แบบตามรุ่นย้อนหลัง ในสตรีครรภ์เดี่ยวที่ตั้งครรภ์ครบกำหนดและมีภาวะอ้วนตามเกณฑ์ของ The Regional Office for Western Pacific Region of WHO (WPRO) BMI criteria for Asians ที่มาฝากครรภ์ ณ โรงพยาบาลหาดใหญ่ รวบรวมข้อมูลจากเวชระเบียน ตั้งแต่ 1 มกราคม 2557 ถึง 31 ธันวาคม 2558 จำนวน 380 คน ประกอบด้วย กลุ่ม obese class I 235 คน (BMI 25-29.9 kg/m^2) และ กลุ่ม obese class II 145 คน (BMI >30 kg/m^2) ภาวะแทรกซ้อนของการตั้งครรภ์ในมารดาและทารกแรกเกิด ในสตรีครรภ์เดี่ยวที่ตั้งครรภ์ครบกำหนดและมีภาวะอ้วนที่น้ำหนักขึ้นตามเกณฑ์และเกินเกณฑ์ตามคำแนะนำของโรงพยาบาลศิริราชจะถูกนำมาวิเคราะห์ทางสถิติ*

ผลการวิจัย: *สตรีครรภ์เดี่ยวที่ตั้งครรภ์ครบกำหนดและมีภาวะอ้วนร่วมกับน้ำหนักขึ้นเกินเกณฑ์ของโรงพยาบาลศิริราช ทั้งกลุ่ม obese class I และ obese class II มีความเสี่ยงที่จะมีทารกตัวโตกว่าอายุครรภ์ น้ำหนักแรกเกิดมากกว่า 4,000 กรัม รวมทั้งมีน้ำหนักแรกเกิดมากกว่ากลุ่มที่น้ำหนักขึ้นตามคำแนะนำของโรงพยาบาลศิริราชอย่างมีนัยสำคัญทางสถิติ สำหรับในมารดาการมีน้ำหนักขึ้นมากกว่าคำแนะนำของโรงพยาบาลศิริราชเพิ่มความเสี่ยงต่อภาวะครรภ์เป็นพิษชนิดรุนแรง ภาวะตกเลือดหลังคลอด การผิดสัดส่วนระหว่างศีรษะทารกกับกระดูกเชิงกราน และเพิ่มอัตราการผ่าตัดคลอด อย่างมีนัยสำคัญทางสถิติ โดยความเสี่ยงจะเพิ่มมากขึ้นในกลุ่ม obese class II*

สรุป: *หญิงที่มีภาวะอ้วนและมีน้ำหนักขึ้นเกินเกณฑ์ตามคำแนะนำของโรงพยาบาลศิริราชจะเพิ่มความเสี่ยงที่จะมีทารกตัวโตกว่าอายุครรภ์ และน้ำหนักแรกเกิดมากกว่า 4,000 กรัม รวมทั้งเพิ่มความเสี่ยงต่อภาวะครรภ์เป็นพิษ ภาวะตกเลือดหลังคลอด การผิดสัดส่วนระหว่างศีรษะทารกกับกระดูกเชิงกราน และเพิ่มอัตราการผ่าตัดคลอด*

คำสำคัญ: *น้ำหนักระหว่างตั้งครรภ์, อ้วน, ผลลัพธ์ของการตั้งครรภ์, คำแนะนำโรงพยาบาลศิริราช*

Introduction

Obesity has become a major health problem worldwide. Developing countries are experiencing increased rate of obesity. World Health Organization (WHO) reported that more than 400 million adults were obese[1], similar to Thailand situation. Thailand National Health Examination Survey reported a significant increase in the prevalence of overweight and obesity, from 25% in 1991 to 48% in 2004 in a sample of Thai adults aged 35–59 years[2].

Obesity can lead to serious diseases and adverse health conditions such as cardiovascular disease, dyslipidemia, diabetes mellitus, cerebrovascular disease and hypertension[3]. Obese women who get pregnant may predispose to serious adverse pregnancy outcomes, increased morbidity and mortality rates.

Obese pregnant women may predispose to obstetric complications. Neonatal complications include neonatal large for gestational age (LGA), macrosomia and birth asphyxia. Influence of various factors on the fetal overgrowth were studied such as maternal obesity, gestational diabetes mellitus (GDM), maternal excessive gestational weight gain (GWG), previous neonatal LGA, and ethnicity[4]. Fetal overgrowth increases risks of shoulder dystocia, genital tract lacerations, emergency cesarean delivery and uterine atony. Other adverse maternal complications include the greater requirement of insulin for patients with diabetes, emergency cesarean section, preeclampsia, gestational hypertension, increased placental weight, shoulder dystocia, post-term pregnancy, postpartum hemorrhage (PPH), puerperal infection and prolonged length of hospital stay[5,6]. Moreover, the greater hospital's resources are used according to increased pregnancy complications.

Because body size of Asian women were smaller than Western women, the Regional office for Western Pacific Region of WHO (WPRO) proposed BMI criteria for Asians[7], obesity was defined as BMI more than or equal to 25 kg/m^2, which suitable for Thai women. Obesity was further classified into 2 subgroups, obese class I (BMI: 25-29.9 kg/m^2) and obese class II (BMI more than or equal to 30 kg/m^2).

Excessive GWG can lead to adverse obstetric complications, such as preeclampsia, GDM and increased cesarean section rate[8]. However excessive GWG is one of the preventable causes, especially in obese woman. In 2009 The Institute of Medicine (IOM) published the recommendations for pregnancy weight gain[9]. Overweight patients should have GWG about 7-11 kg and obese patients (all classes) should have GWG about 7-9 kg. Based on the updated IOM recommendations, less than half of the Thai pregnant women gained optimal weight according to these recommendations[10].

In 2014, the most recent recommendations for GWG in Thai population, Siriraj recommendations for GWG were published. Optimal GWG for obese class I was 6-14 kg and 4-8 kg for obese class II[10]. However, there were few studies about pregnancy outcomes of obese pregnant women who have GWG followed Siriraj recommendations. This study was performed to evaluate the effect of gestational weight gain on maternal and fetal outcomes according to Siriraj recommendations in Thai obese women.

Materials and Methods

This study was retrospective cohort design, performed at Hatyai Hospital, Songkhla, Thailand. After obtaining approval from Institutional Review Board (protocol number : 64/2559), electronic hospital database and medical record were reviewed (from 1 January 2014 to 31 December 2015). The cohort study for binary data formula was used for sample size calculation. Prepregnant-obese Thai women with singleton pregnancy were included. All patients must attend the antenatal care clinic from the first trimester of pregnancy. Obesity was defined as BMI more than or equal to 25 kg/m^2 according to WPRO criteria for Asians. Participants who were diagnosed prepregnancy

medical conditions were excluded (such as hypertension, diabetes mellitus, thyroid diseases, autoimmune diseases, heart diseases, respiratory diseases, renal diseases etc.). Because GDM may affect neonatal birthweight[11], patients with this condition were also excluded from the study. A two-step approach was used for diagnosed GDM in our institute. The test was performed at first prenatal visit for high risk patients or those at 24-28 weeks. All included participants had to deliver at 37-42 completed weeks. Patients were categorized into two groups according to prepregnancy BMI (obese class I and obese class II). Optimal and excessive GWG in each group followed Siriraj recommendations.

Maternal and neonatal outcomes were evaluated. The following variables were defined as (a) LGA: a birth weight more than or equal to 90th percentile for age, based on birthweight of neonates for gestational age (GA) from the study of The King Chulalongkorn Memorial Hospital[12] (b) Neonatal macrosomia: a birth weight was at least 4 kg (c) Neonatal hypoglycemia: blood glucose <40 mg/dL after delivery. (d) Birth asphyxia: APGAR score less than or equal to 7 points at 1 and 5 minutes after delivery. (e) PPH: blood loss was at least 500 mL after third stage of labor in vaginal delivery and at least 1,000 mL in cesarean delivery. (f) cephalopelvic disproportion (CPD): obstructed labor resulting from disparity between the fetal head size and maternal pelvis followed by WHO partograph based on diagnostic criteria[13] (g) Failed induction of labor: defined as failure to generate regular (e.g. every 3 minutes) contractions and cervical change after at least 24 hours of oxytocin administration, with artificial membranes rupture if feasible[14].

Data were analyzed using the STATA version 13.0. Continuous data was analyzed with Mann-Whitney U Test. Categorical data was analyzed with Chi-Squared and Fisher's Exact test. Results were expressed as the relative risk (RR) with 95% confidence interval (CI). Statistical significance was considered when p value < 0.05.

Results

Three hundred and eighty singleton obese pregnant women were included (Obese class I: 235, Obese class II: 145). The patients were categorized into two subgroups, excessive and optimal GWG. In obese class I group, median total GWG in excessive and optimal GWG patients were 15.5 kg (IQR:14.53, 17.35) and 8 kg (IQR:7, 10), respectively ($p < 0.01$). Likewise, obese class II group, median total GWG in excessive GWG patients was 11 kg (IQR:10, 13.20) while median optimal GWG patients was 6.55 kg (IQR:5, 7.70). P value of this difference was less than 0.01. Baseline characteristics of class I and II obese patients were shown in Table 1.

When compared excessive GWG with optimal GWG group: neonatal LGA, macrosomia and birth weight were statistically significant difference in both obese class I and II patients. In obese class I group, median neonatal birthweight in excessive and optimal GWG patients were 3,290 g (IQR: 3,050, 3,690) and 3,177 g (IQR: 2,915, 3415), respectively. This difference was statistical significance ($p < 0.01$). Likewise, obese class II group, median birth weight in excessive GWG patients was 3,436 g (IQR: 3,030, 3,815) while median optimal GWG patients was 3,060 g (IQR: 2,820, 3,310). Considered in obese class I and II, other neonatal outcomes including hypoglycemia, birth asphyxia, and neonatal intensive care unit (NICU) admission were similar between excessive GWG and optimal GWG group. Detailed information about neonatal complications was presented in Table 2.

Maternal outcomes of obese class I and II were shown in Table 3. Statistically significant higher rate of severe preeclampsia, PPH and cesarean section were presented in excessive GWG when compared with optimal GWG group. CPD was the most common indication for cesarean section in both obese class I and II patients. There were significant higher rate of CPD in excessive GWG group in both obese class I and II patients. Detailed information about maternal outcomes was presented in Table 3.

Table 1. Maternal characteristics of obese class I and obese class II patients.

Characteristics	Obese class I (n=235)			Obese class II (n=145)		
	Excessive GWG (n=105)	Optimal GWG (n=130)	p value	Excessive GWG (n=75)	Optimal GWG (n=70)	p value
Age			0.08[a]			0.32[a]
< 20 years	17 (16.19%)	16 (12.31%)		9 (12.00%)	4 (5.71%)	
20-34 years	79 (75.24%)	90 (69.23%)		57 (76.00%)	54 (77.14%)	
≥ 35 years	9 (8.57%)	24 (18.46%)		9 (12.00%)	12 (17.15%)	
Parity			0.19[a]			0.09[a]
Primiparous	35 (33.33%)	33 (25.54%)		23 (30.67%)	13 (18.57%)	
Multiparous	70 (66.67%)	97 (74.46%)		52 (69.33%)	57 (81.43%)	
GA at first ANC (weeks) median (IQR)	9 (7, 11)	10 (8, 12)	0.33[b]	9 (7, 12)	10 (8, 12)	0.35[b]
Prepregnancy BMI median (IQR)	27.80 (27.50, 28)	27.8 (27.50, 28.19)	0.98[b]	32 (31, 34)	32 (30.43, 34.22)	0.42[b]
GA at delivery (weeks)			0.74[a]			0.49[a]
Early term (37-38^{+6})	39 (37.14%)	47 (36.15%)		29 (38.67%)	29 (41.43%)	
Full term (39-40^{+6})	57 (54.29%)	75 (57.69%)		39 (52%)	38 (54.29%)	
Late term (41-41^{+6})	9 (8.57%)	8 (6.16%)		7 (9.33%)	3 (4.28%)	

[a] Chi-squared, [b] Mann-Whitney U Test

Table 2. Neonatal complications between excessive GWG and optimal GWG.

Outcomes	Obese class I (n=235)				Obese class II (n=145)			
	Excessive GWG (n=105)	Optimal GWG (n=130)	RR (95% CI)	p value	Excessive GWG (n=75)	Optimal GWG (n=70)	RR (95% CI)	p value
Neonatal LGA	46 (43.81%)	28 (21.54%)	2.03 (1.37-3.01)	< 0.01[a]	41 (54.67%)	12 (17.14%)	3.19 (1.83-5.55)	< 0.01[a]
Macrosomia	8 (7.62%)	2 (1.54%)	4.95 (1.07-22.83)	0.05[b]	10 (13.33%)	1 (1.43%)	9.33 (1.22-71.04)	0.01[b]
Hypoglycemia	3 (2.86%)	1 (0.77%)	3.71 (0.39-35.19)	0.33[b]	5 (6.67%)	3 (4.29%)	1.56 (0.39-6.27)	0.72[b]
Birth asphyxia	2 (1.90%)	2 (1.54%)	1.24 (0.18-8.64)	1.00[b]	4 (5.33%)	2 (2.86%)	1.87 (0.35-9.88)	0.68[b]
NICU admission	2 (1.90%)	1 (0.77%)	2.48 (0.23-26.93)	0.59[b]	3 (4.00%)	2 (2.86%)	1.40 (0.24-8.13)	1.00[b]

[a] Chi-squared, [b] Fisher's exact test

Table 3. Maternal complication between excessive GWG and optimal GWG.

Outcomes	Obese class I (n=235)				Obese class II (n=145)			
	Excessive GWG (n=105)	Optimal GWG (n=130)	RR (95% CI)	p value	Excessive GWG (n=75)	Optimal GWG (n=70)	RR (95% CI)	p value
Severe preeclampsia	14 (13.33%)	5 (3.85%)	3.47 (1.29-9.31)	0.01[a]	15 (20.00%)	3 (4.29%)	4.67 (1.41-15.43)	0.01[b]
Genital tract lacerations	5 (4.76%)	3 (2.31%)	2.06 (0.51-8.44)	0.47[b]	4 (5.33%)	1 (1.43%)	3.73 (0.43-32.60)	0.39[b]
Operative vaginal delivery	3 (2.86%)	5 (3.85%)	0.74 (0.18-3.03)	0.74[b]	4 (5.33%)	2 (2.86%)	1.87 (0.35-9.88)	0.68[b]
PPH	9 (8.57%)	2 (1.54%)	5.57 (1.23-25.23)	0.01[b]	9 (12.00%)	1 (1.43%)	8.4 (1.09-64.61)	0.02[b,*]
Cesarean section	36 (34.28%)	14 (10.77%)	3.18 (1.82-5.58)	< 0.01[a]	33 (44.00%)	9 (12.87%)	3.42 (1.77-6.63)	< 0.01[a]
CPD	17 (16.19%)	6 (4.61%)	3.51 (1.43-8.58)	< 0.01[a]	12 (16.00%)	3 (4.29%)	3.73 (1.10-12.68)	0.03[b]
Fetal distress	6 (5.71%)	4 (3.08%)	1.85 (0.54-6.41)	0.35[b]	6 (8.00%)	2 (2.86%)	2.8 (0.59-13.41)	0.28[b]
Failed induction of labour	6 (5.71%)	2 (1.54%)	3.71 (0.77-18.02)	0.14[b]	9 (12.00%)	2 (2.86%)	4.2 (0.94-18.77)	0.06[b]
Previous cesarean section	3 (2.86%)	1 (0.77%)	3.71 (0.39-35.19)	0.33[b]	2 (2.67%)	1 (1.43%)	1.87 (0.17-20.13)	1.00[b]
Others	4 (3.81%)	1 (0.77%)	4.95 (0.56-43.64)	0.18[b]	4 (5.33%)	1 (1.43%)	3.73 (0.42-32.60)	0.37[b]

[a] Chi-squared, [b] Fisher's exact test

Discussion

Neonatal birth weight in excessive GWG group was higher than optimal GWG group with statistical significance in both obese class I and obese class II. The rates of following neonatal complications including neonatal LGA and macrosomia were significant higher in women with excessive GWG, too. Excessive GWG was not only affected the neonatal birth weight, but also affected several maternal outcomes. In this study, there were significant increased incidence of severe preeclampsia, PPH, cesarean section rate, and emergency obstetric conditions due to CPD.

These outcomes were similar to previous studies. Neonatal LGA were associated with fetal and maternal risk[15-17]. Fetal risk included birth trauma, e.g., shoulder dystocia, brachial plexus injury and death[18]. Interestingly, no shoulder dystocia was found in the present study. However, the rate of shoulder dystocia may be affected from difference decision making of the obstetrician in performing cesarean section. Maternal risk for neonatal LGA included genital tract lacerations, prolonged labor, uterine atony and increased cesarean section rate[19]. The risk that mentioned above was related to increased incidence of life threatening complications and hospital expenses, especially PPH.

At two hours after delivery, there was no statistically significant difference in the incidence of

neonatal hypoglycemia between two groups in obese class I and obese class II. This finding was different from the study of Stotland et al., which reported significant higher incidence of neonatal hypoglycemia in excessive GWG group[20]. The incidence of neonatal hypoglycemia might be affected from subclinical insulin resistance mentioned in Stotland's study. However, early breast feeding policy in our institute might prevent hypoglycemia in neonates. Other adverse neonatal outcomes such as birth asphyxia and NICU admission rate were not statistically significant difference between two groups.

Because obesity and excessive GWG were characterized by insulin resistance, causing inflammation and endothelial activation, excessive GWG in obese pregnant women was associated with preeclampsia. The volume of extracellular fluid, manifest as edema, is usually much greater than that in normal pregnant women. The mechanism responsible for pathological fluid retention is thought to be endothelial injury[21]. Thus this may increased incidence of preeclampsia in excessive GWG. This hypothesis was supported by the increased rate of preeclampsia in obese pregnant women. It increases from 1.4% in women with normal prepregnancy BMI to 2.5% in those with BMI 25-29.9 kg/m^2 and 4.7% in those with BMI greater than or equal to 30 kg/m^2 [22]. Moreover, Swank et al reported higher frequencies of preeclampsia in excessive GWG patients with statistical significance[23], as same as findings from our study. Cesarean section rate was related to excessive GWG and obesity. The most common obstetric indication for cesarean section was CPD. One reason was obese pregnant women tend to increased thickness of pelvic soft tissue, resulting in a narrow birth canal[24]. In addition, obese pregnant women were susceptible to have LGA that could not easily passed birth canal.

Moreover, cesarean section also increased risk of infections, damage of adjacent organs and bleeding from uterine atony and laceration. At the same time, cesarean section was associated with complications from regional and general anesthesia. Incidence of other adverse maternal outcomes such as genital tract lacerations and operative vaginal delivery were not significant difference between two groups.

PPH was a one of significant associated factor, regardless of route of deliveries. It had highest relative risk in both obese class I and II comparing with other factors. PPH was multifactorial causes, the results might be confounded by increased cesarean section rate, and obstetric injuries from large fetus. However, avoid excessive GWG brought to decrease risk of PPH, a life-threatening condition.

IOM recommendations on GWG were appropriate for western population. In 2014, Siriraj recommendations were published and applied for Asian pregnant women, especially Thai population. There were few studies about pregnancy outcomes according to Siriraj recommendations. We followed GWG of obese pregnant women based on this guideline and pregnancy complications were evaluated.

In Thailand, the impact of prepregnancy BMI for obese pregnant has not been well studied. Several studies demonstrated that body size of Thai population was smaller than western population, so BMI greater than or equal to 25 kg/m^2 was appropriate cut-off point for obesity in Thai population. The study of Pongchaiyakul et al supported this cut-off point because percentage of body fat in Thai population at BMI greater or equal to 25 kg/m^2 were not different from obese Caucasian populations[25].

The Siriraj recommendations for GWG are applicable to obese Asian women because their body sizes were similar to pregnant Thai women. Moreover, Siriraj recommendations for GWG are effective as IOM recommendations, supported by the present study results. The authors compared adverse maternal outcomes between the patients whom GWG according to Siriraj recommendations and IOM recommendations were archived, the results were equivalent. From the reasons that mentioned above, pregnant Thai women should have GWG be in line with Siriraj recommendations.

Obesity and excessive GWG were preventable. Ida et al., reported that appropriate nutritional care,

advice and body weight follow-up not only controlled GWG but also significantly reduced emergency cesarean section rate and postpartum weight retention[26]. Weight control and nutritional care during pregnancy were beneficial for obese pregnant women. Multidisciplinary teams can use this result for counseling obese women about preconception planning, diet, and physical activities for prevent intrapartum and postpartum complications. The present study collected clinical data based on Thai population. The results can be used as reference outcomes for obese Asian pregnant women which body size were proportionate to obese Thai pregnant women.

Siriraj recommendations and IOM guidelines yielded similar pregnancy outcomes, including neonatal and maternal outcomes. The proportion of subjects who gained optimal weight according with Siriraj recommendations and IOM recommendations was 60% and 40%, respectively. Similar to Siriraj recommendations, this study not only showed high cesarean section rate, incidence of severe preeclampsia and low operative vaginal deliveries, but also displayed high incidence of LGA. Following Siriraj recommendations, bad outcomes seem to be decreased. It could be implied that these recommendations are suitable for Thai obese women.

Retrospective design was a limitation of this study. This observational study was not addressing the long-term neonatal and maternal outcomes. Future study may be performed to explore long-term complications of excessive GWG.

Conclusion

obese Thai women with term-singleton pregnancy who was diagnosed excessive GWG according to Siriraj recommendations were associated with increased risk of neonatal LGA, macrosomia and higher birth weight. Adverse maternal outcomes were also greater including severe preeclampsia, CPD, cesarean section rate and PPH. Siriraj recommendations for GWG is applicable to obese Thai pregnant women, including obese Asian pregnant women.

Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Intrauterine Misoprostol Plus Intravenous Oxytocin for Reduction of Blood Loss in Cesarean Delivery

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ABSTRACT

Objectives: To evaluate the efficacy of using intrauterine misoprostol combined with oxytocin intravenous infusion to reduce intraoperative blood loss and prevent postpartum hemorrhage in cesarean section.

Materials and Methods: Efficiency research, randomized control trial was conducted in 222 term pregnant women who admitted for cesarean section in any indications as defined at Phayao hospital between October 1, 2016 and December 31, 2016. All pregnant women received 20 units of oxytocin by intravenous infusion immediately after delivery of the baby. Eight hundred micrograms misoprostol were inserted at both sides of uterine cornu after placental delivery in treatment group by random assignment. The treatment outcomes were measured by volume of intraoperative blood loss, preoperative and postoperative hemoglobin and hematocrit levels, requirements for additional uterotonic drugs and side effects related to misoprostol.

Results: Intrauterine misoprostol combined with oxytocin intravenous significantly reduced the estimated intraoperative blood loss when compared with oxytocin intravenous only (418.5 ± 153.0 ml vs 647.4 ± 244.8 ml, $p < 0.001$). There was also a reduction of the total blood loss within 24 hours postoperative which was measured by the difference of hemoglobin/hematocrit levels preoperatively and postoperatively (0.9 g/dl (0.3-1.4) vs 1 g/dl (0.4-1.8), $p = 0.032$ and 2.4%(1.1-4.2) vs 3.0%(1.4-5.6), $p = 0.024$ respectively). Furthermore additional uterotonic drug requirements (2.7% vs 9.0%, $p = 0.041$) and operative time also decreased (24.2 ± 8.4 mins vs 27.1 ± 12.5 mins, $p = 0.046$). However, maternal fever was detected within 24 hours postoperative (≥ 38°C) (66.7% vs v38.7%, $p < 0.001$).

Conclusion: Intrauterine misoprostol combined with oxytocin infusion during cesarean section could reduce intraoperative blood loss, prevent postpartum hemorrhage and reduce any additional uterotonic drug requirements. A minor side effect such as fever was identified which subsided spontaneously within 24 hours.

Keywords: intrauterine misoprostol, intraoperative estimated blood loss, cesarean section, postpartum hemorrhage

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การใช้ยา misoprostal ทางมดลูกร่วมกับยา oxytocin หยดทางน้ำเกลือเพื่อลดอัตราการสูญเสียเลือดในขณะผ่าตัดคลอด

วิราวรรณ ราศรี

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประเมินประสิทธิภาพของการบริหารยา Misoprostol ทางมดลูก ร่วมกับยา Oxytocin หยดทางน้ำเกลือในการช่วยการสูญเสียเลือดในขณะผ่าตัดคลอดและป้องกันภาวะตกเลือดหลังคลอด*

วัสดุและวิธีการ: *เป็นการศึกษาแบบ efficiency research โดยการศึกษาแบบสุ่ม (Randomised Control Trial) ศึกษาที่โรงพยาบาลพะเยา ระหว่างวันที่ 1 ตุลาคม 2559 ถึง 31 ธันวาคม 2559ในมารดาตั้งครรภ์ครบกำหนดที่เข้ารับการผ่าตัดคลอดด้วยข้อบ่งชี้ต่างๆ ตามกำหนด แบ่งแบบสุ่มเป็น 2 กลุ่ม คือกลุ่มที่ได้รับยา misoprostol ขนาด 800 ไมโครกรัม สอดทางมดลูก และอีกกลุ่มไม่ต้องสอดยา ทั้งสองกลุ่มจะได้รับยา oxytocin ขนาด 20 ยูนิต หยดทางน้ำเกลือทันทีหลังทารกคลอด ประเมินปริมาณเลือดที่สูญเสียในระหว่างผ่าตัด การเปลี่ยนแปลงของค่าฮีโมโกลบินและฮีมาโตคริตก่อนผ่าตัด และ 24 ชั่วโมงหลังผ่าตัด ความจำเป็นในการใช้ยากระตุ้นการแข็งตัวของมดลูกชนิดอื่นร่วมในการช่วยการแข็งตัวของมดลูกในระหว่างผ่าตัด และผลข้างเคียงของยา misoprostol*

ผลการศึกษา: *การบริหารยา misoprostol ทางมดลูกร่วมกับ oxytocin หยดทางน้ำเกลือ ช่วยลดปริมาณเลือดที่สูญเสียในระหว่างผ่าตัดเมื่อเปรียบเทียบกับการให้ oxytocin หยดทางน้ำเกลือเพียงอย่างเดียว (418.5 ± 153.0 มล. และ 647.36 ± 244.77 มล., $p < 0.001$) นอกจากนี้ยังลดปริมาณเลือดที่สูญเสียทั้งหมดหลังผ่าตัด โดยวัดจากการเปลี่ยนแปลงของค่าฮีโมโกลบินและฮีมาโตคริตก่อนและหลังการผ่าตัด (0.9 ก/ดล.(0.3-1.4) และ1 ก/ดล.(0.4-1.8), $p = 0.032$ และ 2.4% (1.1-4.2) และ 3.0% (1.4-5.6), $p = 0.024$ ตามลำดับ) ความจำเป็นในการใช้ยากระตุ้นการแข็งตัวของมดลูกชนิดอื่นร่วมในการช่วยการแข็งตัวของมดลูกในระหว่างผ่าตัด (2.7% และ 9.0%, $p = 0.041$) และระยะเวลาในการผ่าตัด (24.2 ± 8.4 นาที และ 27.1 ± 12.5 นาที, $p = 0.046$) แต่พบจำนวนมารดาผ่าตัดคลอดมีไข้หลังผ่าตัดภายใน 24 ชั่วโมง (≥ 38°C) (66.7% และ 38.7%, $p < 0.001$)*

สรุป: *การบริหารยา misoprostol ทางมดลูกร่วมกับ oxytocin หยดทางน้ำเกลือช่วยลดปริมาณเลือดที่ต้องสูญเสียในระหว่างผ่าตัด ลดการเกิดภาวะตกเลือดหลังคลอด ลดความจำเป็นในการใช้ยากระตุ้นการแข็งตัวของมดลูกชนิดอื่น และลดระยะเวลาในการผ่าตัด แต่พบผลข้างเคียง คือไข้มากกว่าหรือเท่ากับ 38°C ในระยะหลังผ่าตัดใน 24 ชั่วโมงแรก*

คำสำคัญ: *การบริหารยา misoprostol ทางมดลูก, การประเมินการสูญเสียเลือดในขณะผ่าตัด, การผ่าตัดคลอด, ภาวะตกเลือดหลังคลอด*

Introduction

Postpartum hemorrhage from uterine atony is the leading cause of preventable maternal mortality which is found in both vaginal and cesarean deliveries. Nowadays, cesarean section is increasing in both developed and developing countries[1-8]. Prevention of postpartum hemorrhage in this group is important to safe maternal life. Oxytocin has been routinely used to prevent uterine atony and excessive uterine bleeding during cesarean delivery. However, despite its effectiveness, 10-40% of cases need additional uterotonic drugs to gain good uterine contraction[9,10]. The most common additional uterotonic agent is methyl ergometrine. Methylergonovine (Methergine) is an ergot alkaloid that causes generalized smooth muscle contraction of the uterus and induce contract tetanically[11]. A typical dose of methylergonovine is 0.2 mg intramuscularly and may be repeated as required at intervals of two to four hours. Adverse effects include nausea, vomiting, stomach pain, diarrhea, leg cramps, skin rash, headache, increased sweating and dizziness. Ergot alkaloid agents may increase blood pressure rapidly so they are contraindicated in women with preeclampsia and hypertension. However, the disadvantage of this agent is dose related.

Misoprostol is a prostaglandin E1 analogue with good uterotonic properties and few adverse effects at therapeutic dose. It can be used oral, sublingual, buccal, rectal and intrauterine[9,12-17]. According to its availability, low cost, thermal stability, and ease of administration, it is suitable for worldwide use even in low resource settings in developing countries[12]. There have been many randomized controlled trials studied in efficacy of intraoperative misoprostol in any routes to reduced blood loss and prevent postpartum hemorrhage. They found that using misoprostol had similar efficacy as oxytocin[9,12-15]. But Zhao, et al., reported misoprostol had more efficacy to reduce blood loss than oxytocin[16]. Hower, a study in Mexico using misoprostol intrauterine combined with oxytocin intravenous compared to oxytocin intravenous alone, showed more efficacy in reduced blood loss in cesarean section[17]. The aim of this study was to find out the effectiveness of misoprostol application by intrauterine route in the aspect of decreasing blood loss, and side effects.

Materials and Methods

This prospective randomized controlled trial was conducted at Phayao Hospital. After approved by the ethics committee of Phayao Hospital, all term pregnant women underwent emergency or elective cesarean section from any indications were enrolled. Informed consent was taken from all subjects. The exclusion criteria were twin pregnancy, pregnancy with obstetric hemorrhage such as placenta previa, placental abruption and vasa previa, pregnancy with coagulopathy or thrombocytopenia or blood dyscrasias, and pregnancy induced hypertension (PIH) with hemolysis, elevated liver enzyme, and low platelets (HELLP) syndrome, with a history of prostaglandin allergy and current medication which could cause severe drug interaction to prostaglandins such as dinoprostone topical, magnesium-containing antacids and quinapril. The sample size was calculated from a pilot study as mean with standard deviation (SD) of intraoperative blood loss compared between two groups of misoprostol intrauterine plus oxytocin intravenous (552.4 ±1 99.8 ml) and oxytocin intravenous only (651.1 ± 248.7 ml), and the power of the test was 90%. The sample size in each group was 111 women. All women were assigned randomly to one of two study groups using a lottery by the midwifery. The first group received 800 micrograms of misoprostol intrauterine inserted at cornual part bilaterally, divided into 400 micrograms in each side after placental delivery combined with 20 units of oxytocin infusion. The second group received 20 units of oxytocin infusion only after delivery. The dose of oxytocin was 20 units plus 1,000 ml of 0.9% normal saline solution started with 250 ml in 10 minutes (0.5 units /min) and then 120 ml/hr (0.04 units /min) for 6 hours. The same standard operation of all obstetricians in our department was performed for all pregnant women. The main outcome measurements were volume of intraoperative blood loss and the different measurement in hemoglobin/hematocrit levels

preoperative and 24 hours after operation. Intraoperative blood loss was measured by blood in the suction apparatus after operation plus the different weight of abdominal swabs and gauzes before and after operation. We calculated 1 gram of the different weight equal to 1 ml of blood loss. Postoperative drop in hemoglobin/hematocrit was calculated by the difference between preoperative (when the women were admitted) and 24 hours postoperative (from incision time) from the central lab. Other outcome measurements were requirement of additional uterotonic agents, misoprostol related side effects which included shivering, pyrexia, nausea, vomiting and headache, blood transfusion within 24 hours postoperative and antiemetic drugs for symptomatic supported when indicated. Adverse effects and antiemetic drugs were recorded within 6 hours after operation except fever that was recorded within 24 hours after operation by the anesthesiologists and postpartum ward nurses. Pyrexia and hyperpyrexia were defined as temperature higher than 38°C and 40°C respectively. Intrauterine misoprostol route was defined by insertion of misoprostol into the uterine cornu at both sides after placental delivery. Intravenous infusion of oxytocin 20 units in 1,000 ml saline solution was started at 0.5 unit/min for 10 min, followed by 0.04 unit/min for 6 hours after delivery (2.4 units/hr). Additional uterotonic agents were used by the obstetricians based on clinical findings during surgery and recorded by anesthesiologists.

Statistical Analysis

Categorical variables were reported as count and percentage and analyzed by chi-square test or Fisher's exact test based on expected value. Continuous variables were reported as mean with SD and analyzed by Student's t-test and rank sum test depended on data distribution. Power of the test < 0.05 was considered as the level of significance. Data distributions were tested using histogram or Shapiro wilk test.

Results

A total of 222 term pregnant women underwent emergency or elective cesarean section of any indications as defined. Randomly sampling by midwifery into two groups, 111 pregnant women received misoprostol intrauterine combined with oxytocin infusion and 111 pregnant women received only oxytocin infusion. There was no statistically differences between the two groups with regard to maternal age, gestational age, gravidity, parity, risk factors, indications for surgery, types of skin incision, types of operations, types of anesthesia and neonatal birth weight (Table 1, 2).

Table 1. General characteristics of term pregnant women who underwent cesarean section compared between the intrauterine misoprostol plus intravenous oxytocin group and the intravenous oxytocin only group.

Basic characteristics	Oxytocin IV (n=111)	Oxytocin IV+ Misoprostol IU (n=111)	p value
maternal age(mean ± SD)	29.3 ± 6.2	28.8 ± 5.6	0.570
Gravida(mean ± SD)	1.7 ± 0.8	1.8 ± 0.9	0.478
Parity (median (IQR))	1.0 (0.0-1.0)	0.0 (0.0-1.0)	0.820
GA(mean ± SD)	38.8 ± 0.8	38.1 ± 0.8	0.135
Birth weight(mean ± SD)	3111.1 ± 384.3	3023.7 ± 398.2	0.098

SD: standard deviation

Table 2. The numbers of term pregnant women undergoing cesarean section in risk factors, indications for cesarean section, types of skin incision, types of operation and types of anesthesia compared between the intrauterine misoprostol plus intravenous oxytocin group and the intravenous oxytocin only group.

Basic characteristics	Oxytocin IV (n=111)		Oxytocin IV + misoprostol IU (n=111)		p value
	N	%	N	%	
Risk factors					0.067
- None	45	40.5	53	47.8	
- Elderly gravida	10	9.1	11	9.9	
- Previous C/S	25	22.5	32	28.8	
- Others	31	27.9	15	13.5	
Indication					0.815
- Previous C/S	38	34.2	35	31.5	
- Maternal request C/S	26	23.4	32	28.8	
- CPD	21	19.0	18	16.3	
- Others	26	23.4	26	23.4	
Type of skin incision					0.369
- Pfannenstiel	87	78.4	90	81.1	
- Low midline	24	21.6	21	18.9	
Operation					0.467
- C/S	74	66.7	79	71.2	
- C/S with TR	37	33.3	31	27.9	
- C/S with TR with appendectomy	0	0.0	1	0.9	
Anesthetic type					0.447
- General anesthesia	55	49.6	57	51.4	
- Spinal anesthesia	56	50.5	54	48.7	

C/S: cesarean section, CPD: cephalopelvic disproportion, TR: tubal resection

Other risk factors including teenage pregnancy, fetal growth restriction, pregnancy induced hypertension, maternal with medical history such as hypertension, diabetes mellitus, thyrotoxicosis, hypothyroid, maternal anemia and/or thalassemia, human immunodeficiency virus in pregnancy, breech presentation and pregnancy with oligohydramnios.

Other indications for cesarean section including fetal distress, non-reassuring fetal status or fetal heart rate pattern, breech presentation, elderly gravida, failed induction, unprogressed labor.

This study showed that the mean estimated blood loss was statistically significant lower in the misoprostol group (418.5 ± 153.0 ml vs 647.4 ± 244.8 ml, $p < 0.001$). Mean Hemoglobin and Hematocrit level changed was also statistically significant lower in misoprostol group 0.9 g/dl (0.3-1.4) vs 1 g/dl (0.4-1.8), $p = 0.032$ and 2.4 % (1.1-4.2) vs 3.0 % (1.4-5.6), $p = 0.024$ respectively). Similarly, the mean operative time was significantly decreased in the misoprostol group (24.2 ± 8.4 min vs 27.1 ± 12.5 min, $p = 0.046$) (Table 3).

Table 3. Comparison of mean intraoperative estimated blood loss, mean decrease in hemoglobin and hematocrit level within 24 hours postoperative and mean operative time between the intrauterine misoprostol plus intravenous oxytocin group and the intravenous oxytocin only group.

Indicators	Oxytocin IV (n=111)	Oxytocin IV + misoprostol IU (n=111)	p value
Mean intraoperative blood loss (ml) (mean ± SD)	647.4±244.8	418.5±153.0	< 0.001
Median fall in hemoglobin (g/dl) median (IQR)	1(0.4-1.8)	0.9(0.3-1.4)	0.032
Median fall in hematocrit (%) median (IQR)	3.0(1.4-5.6)	2.4(1.1-4.2)	0.024
Operative time (min) (mean ± SD)	27.1±12.5	24.2±8.4	0.046

SD: standard deviation, IQR: interquartile range

The percentage of cases who had blood loss more than 500 and 1000 ml were significantly lesser in the misoprostol group (25.2% vs 70.3%, p < 0.001 and 0.9% vs 8.1%, p < 0.001 respectively). Similarly, the numbers of women who needed additional uterotonic agents was also lesser in the misoprostol group than in the oxytocin only group (2.7% vs 9.0%, p = 0.041) (Table 4).

Pyrexia (body temperature higher than 38°C) was significantly higher in the misoprostol group (66.7% vs 38.7%, p < 0.001). However, no high grade fever over 40°C was reported in any pregnant women. There was no statistically difference in shivering, nausea, vomiting, and numbers of women who need blood transfusion or antiemetic drugs between two groups (Table 4).

Table 4. Numbers of pregnant women who had blood loss more than 500 and 1,000 ml during surgery, who need of additional uterotonic drugs use, who need blood transfusion within 24 hours postoperative, who had adverse effects such as nausea, vomiting, headache, shivering and fever (≥ 38°C and ≥ 40°C) compared between intrauterine misoprostol plus intravenous oxytocin group and intravenous oxytocin only group

Indicator	Oxytocin IV (n=111)		Oxytocin IV + misoprostol IU (n=111)		p value*
	N	%	N	%	
- Blood loss ≥ 500 ml	78	70.3	28	25.2	< 0.001
- Blood loss ≥ 1000 ml	9	8.1	1	0.9	< 0.001**
- Use of additional uterotonic agents	10	9.0	3	2.7	0.041
- Blood transfusion	3	2.7	0	0.0	0.123**
- Shivering	0	0.0	2	1.8	0.500**
- Nausea / Vomiting	5	4.5	3	2.7	0.500**
- Headache	-	-	-	-	-
- Pyrexia (≥ 38°C)	43	38.7	74	66.7	<0.001
- Hyperpyrexia (≥ 40°C)	-	-	-	-	-
- Antiemetic drug	11	9.9	5	4.5	0.097**

* Chi-square test, ** Fisher's exact test

Discussion

It is well known as cesarean section is an obstetric procedure that increasing worldwide in both developed and developing countries. Oxytocin is used routinely to prevent uterine atony during surgery. But in some area, further uterotonic drugs were added on to prevent the bleeding problem[9,10]. Methyl ergometrine is usually chosen as a first common additional uterotonic agent but because of its adverse effects, many researches try to find out other uterotonic agents for helping uterine contraction in order to reduce blood loss. One of drugs is misoprostol in any routes. From previous systematic review and meta-analysis[26], there have been many researches try to study about misoprostol in any routes to reduce blood loss during operation for prevent postpartum hemorrhage. Chaudhuri, et al reported rectal route had a significantly reduced intraoperative and postoperative blood loss[20] but no statistically different in oral or sublingual routes when compared to oxytocin intravenous use[9,12,14,18,19]. Misoprostol rectal route plus intravenous oxytocin reduced intraoperative and postoperative blood loss, mean decrease in hemoglobin/hematocrit level postoperative and need for additional uterotonic agents[21]. Sublingual route plus intravenous oxytocin reduced mean fall in hemoglobin/hematocrit postoperative and need for additional uterotonic agents[22,23,25]. In addition, El Tahan, et al showed sublingual route had significantly lesser in intraoperative blood loss[25]. Buccal route plus intravenous oxytocin reduced the need for additional uterotonic agents only[13]. Oral route plus intravenous oxytocin found no statistically difference in decreasing intraoperative blood loss or postpartum hemorrhage. And the study from Mexico reported the same study results misoprostol intrauterine plus oxytocin intravenous use reduced mean decrease in hemoglobin/hematocrit level postoperative only[17]. On the other hand, they found the proportion of women had shivering more than intravenous oxytocin only group[17]. In this meta-analysis, they found misoprostol combined with oxytocin appeared to be more effective than oxytocin alone in reducing intraoperative and postoperative hemorrhage during cesarean section. There were no significant differences in intraoperative and postoperative hemorrhage when misoprostol was compared to oxytocin[26]. Except Chaudhuri, et al that studied misoprostol rectal route compared to intravenous oxytocin found the same result of reduction of blood loss[20]. Most of the studies in this meta-analysis found the adverse effects were shivering and fever more than intravenous oxytocin only group[9,12-16,18-25] especially either in sublingual route only or in combination.

In this study, we chose intrauterine route of misoprostol because it was simple and easier way to do in case of cesarean section than other routes such as oral, sublingual, buccal or rectal. Besides that, it could use in all cases either general or spinal anesthesia and less contamination when compared to rectal route. By the way, pharmacology of misoprostol, a prostaglandin analogue, binds to myometrial cells to cause strong myometrial contractions that start at the fundus near a cornu and propagate down to the body of uterus leading to expulsion of tissue and reduce postpartum hemorrhage. So, we thought that insertion at uteri cornu was simple and easily to fix the tablets. It might help in their absorption to myometrial cells. One paper from Mexico studied in this route, they found intrauterine misoprostol plus intravenous oxytocin reduced mean decrease in hemoglobin/hematocrit level postoperative and had some minimal side effect. In our study, we found that there was no statistically difference between two groups with regard to maternal age, gestational age, gravidity, parity, risk factors, indications for surgery, types of skin incision, types of operations, types of anesthesia and neonatal birth weight. The result showed 800 microgram of misoprostol inserted at the cornual part of the uterus both sides plus 20 units of intravenous oxytocin infusion was significantly decrease in intraoperative blood loss and postpartum hemorrhage (blood loss more than 1000 ml) that is a serious obstetric

complication caused maternal morbidity and mortality. Like the study of Chaudhuri, et al., used rectal route of misoprostol[20], Elsedeek MS in rectal route plus oxytocin intravenous[21] and El Tahan, et al., in sublingual route that found significantly reduced intraoperative and postoperative blood loss[25]. Similarly with previous studies of Quiroga Díaz, et al., Chaudhuri, et al., Elsedeek, Fekih, et al., Chalermpolprapa, Sood, et al ., and El Tahan, et al., the study results showed significantly decreased in mean decrease in hemoglobin/hematocrit level postoperative[17,20-25]. Besides significantly decreased in requirement of additional uterotonic drugs likes the study of Fekih, et al, Chalermpolprapa, Sood, et al., and El Tahan, et al[22-25]. Additionaly, operative time also consequential decreased in our study. In adverse effects of misoprostol, there was no statistically difference in nausea, vomiting, shivering, headache between two groups except body temperature more than 38°C but not higher than 40°C 24 hours postoperative was higher in this group than intravenous oxytocin only like the results of many previous studies[9,12-16,18-25]. Dose-related fever should be further investigated to minimize the adverse effect. Furthermore intrauterine misoprostol plus intravenous oxytocin significantly reduced the proportion of women need antiemetic drugs use and need for blood transfusion.

Conclusion

Intrauterine misoprostol combined with oxytocin infusion during cesarean section could reduce intraoperative blood loss, prevent postpartum hemorrhage and any additional uterotonic drugs requirement. Minor side effect such as fever was identified which subsided spontaneously within 24 hours.

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Potential conflicts of interest

The author declares no conflict of interest.

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OBSTETRICS

Nipple Characteristics between Teenage and Adult in Postpartum Period and Success in Breastfeeding at day 3 Postpartum

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ABSTRACT

Objectives: To compare nipple length and diameter between teenage and adult mothers during early postpartum period and their association with success in breastfeeding at day 3 postpartum.

Materials and Methods: A total of 315 nulliparous women, who delivered at Siriraj Hospital between March and October 2016 were enrolled. Study group consisted of 105 teenage mothers and 210 adult mothers were served as a comparison group. Baseline characteristics, obstetric data, maternal and neonatal outcomes were extracted from medical records. Nipple length and diameter were measured. LATCH score was used to evaluate success in breastfeeding at day 3 postpartum, using score of ≥ 7 as a cut off. Comparisons of various characteristics were made between groups. Association between nipple characteristics and LATCH score were evaluated.

Results: Teenage mothers were significantly more likely to be underweight, working as a housewife, and have lower income. While gestational age at delivery was comparable, teenage mothers were significantly more likely to deliver vaginally. Birth weight were significantly lower among teenage mother. Nipples of teenage mothers were significantly shorter and narrower than adult mothers (7.3 ± 2.8 mm vs. 9.6 ± 2.8 mm, $p < 0.001$ and 13.5 ± 1.4 mm vs. 14.2 ± 1.8 mm, $p = 0.002$, respectively). At day 3 postpartum LATCH scores ≥ 7 were comparable between groups (58.1% vs. 55.2%, $p = 0.631$). Nipple length of ≥ 7 mm was significantly associated with success in breastfeeding at day 3 postpartum (LATCH score of ≥ 7) in both teenage (71% vs. 39.5%, $p = 0.002$) and adult (60.4% vs. 13%, $p < 0.001$) mothers.

Conclusion: Teenage nipples had significantly shorter and narrower than adult mothers. Pregnant women with nipple length of ≥ 7 mm on at least one side significantly increased the chance of success in breastfeeding at day 3 postpartum regardless of age group.

Keywords: nipple length, nipple width, teenage pregnancy, breastfeeding.

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ลักษณะของหัวนมในมารดาวัยรุ่นเทียบกับมารดาวัยผู้ใหญ่ในระยะหลังคลอด และความสำเร็จในการให้นมบุตรในวันที่ 3 หลังคลอด

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบลักษณะของหัวนมในมารดาวัยรุ่น เทียบกับมารดาวัยผู้ใหญ่ในระยะหลังคลอด และศึกษาความสัมพันธ์ของลักษณะหัวนมกับความสำเร็จในการให้นมบุตรในวันที่ 3 หลังคลอด

วัสดุและวิธีการ: ทำการศึกษาสตรีหลังคลอดครรภ์แรกที่ไม่มีข้อห้ามในการให้นมบุตรจำนวน 315 ราย ที่มาคลอดที่โรงพยาบาลศิริราช โดยแบ่งเป็นกลุ่มมารดาวัยรุ่นจำนวน 105 ราย และมารดาวัยผู้ใหญ่จำนวน 210 ราย เก็บรวบรวมข้อมูลทั่วไป ข้อมูลด้านสูติศาสตร์ ข้อมูลการคลอด และผลของการตั้งครรภ์ ทำการตรวจประเมินลักษณะหัวนม โดยใช้ Syringe และไม้บรรทัดที่มีรูกลม ที่มีมาตรวัดในหน่วยมิลลิเมตร วัดขนาดความยาวและความกว้างหัวนมทั้งสองข้างหลังจากได้รับการกระตุ้นหัวนม ระหว่าง 24-48 ชั่วโมงหลังคลอด และทำการประเมินความสำเร็จในการให้นมบุตรด้วย LATCH scores ในวันที่ 3 หลังคลอด โดยใช้จุดตัดที่คะแนน ≥ 7 ทำการเปรียบเทียบข้อมูลทั่วไป และลักษณะของหัวนมระหว่างกลุ่มมารดาวัยรุ่นเทียบกับมารดาวัยผู้ใหญ่ และศึกษาความสัมพันธ์ของลักษณะหัวนมกับความสำเร็จในการให้นมบุตรโดยเปรียบเทียบ LATCH scores ระหว่าง 2 กลุ่ม

ผลการศึกษา: มารดาวัยรุ่นมีน้ำหนักก่อนตั้งครรภ์ต่ำกว่าเกณฑ์ มีอาชีพแม่บ้าน มากกว่า และมีรายได้ต่ำกว่า มารดาวัยผู้ใหญ่อย่างมีนัยสำคัญทางสถิติ อายุครรภ์เฉลี่ยเมื่อคลอด ไม่แตกต่างกันระหว่าง 2 กลุ่ม แต่มารดาวัยรุ่นมีอุบัติการณ์ในการคลอดทางช่องคลอดสูงกว่าอย่างมีนัยสำคัญทางสถิติ น้ำหนักทารกแรกคลอดในมารดาวัยรุ่นต่ำกว่ามารดาวัยผู้ใหญ่อย่างมีนัยสำคัญทางสถิติ พบว่าหัวนมในกลุ่มมารดาวัยรุ่นสั้น และแคบกว่ากลุ่มมารดาวัยผู้ใหญ่อย่างมีนัยสำคัญทางสถิติ (7.3 ± 2.8 มิลลิเมตร และ 9.6 ± 2.8 มิลลิเมตร, p < 0.001 และ 13.5 ± 1.4 มิลลิเมตร และ 14.2 ± 1.8 มิลลิเมตร, p=0.002 ตามลำดับ) พบว่าคะแนน LATCH scores ≥ 7 ไม่แตกต่างกันระหว่าง 2 กลุ่ม (58.1% และ 55.2%, p=0.631) และพบว่าความยาวหัวนม ≥ 7 มม. สัมพันธ์กับความสำเร็จในการให้นมบุตร อย่างมีนัยสำคัญทางสถิติในทั้งกลุ่มวัยรุ่น (71% และ 39.5%, p=0.002) และกลุ่มวัยผู้ใหญ่ (60.4% และ 13%, p<0.001)

สรุป: หัวนมของกลุ่มมารดาวัยรุ่นหลังคลอด สั้น และแคบกว่ากลุ่มมารดาวัยผู้ใหญ่อย่างมีนัยสำคัญทางสถิติ และหญิงตั้งครรภ์ที่มีความยาวหัวนมข้างใดข้างหนึ่ง ≥ 7 มิลลิเมตร เพิ่มโอกาสความสำเร็จในการให้นมบุตรอย่างมีนัยสำคัญทางสถิติทั้งกลุ่มมารดาวัยรุ่นและวัยผู้ใหญ่

คำสำคัญ: ความยาวหัวนม, ความกว้างหัวนม, หญิงตั้งครรภ์วัยรุ่น, การให้นมบุตร

Introduction

Adolescents involve more than 18% of all Thais[1]. The 2014 World Health Statistic indicate that the average global birth rate among 15 to 19 years old is 49 per 1,000 girls[2]. Teenage pregnancy is an important health issue worldwide. They are at increased risk of developing many complications during pregnancy and childbirth such as pregnancy induced hypertension, anemia, preterm birth, cephalopelvic disproportion, and postpartum breastfeeding problems[3].

The World Health Organization (WHO) recommends mothers worldwide to exclusive breastfeed for the child's first 6 months to achieve optimal growth, development and health. Among adolescent mothers, many factors have been related to unsuccessful breastfeeding, such as primiparity and cesarean delivery[4,5]. Maternal age has been reported to be directly associated with the duration of breastfeeding that adolescents have low breastfeeding initiation rates, as well as a short duration of breastfeeding[6]. In a previous review, studies indicated that adolescents breastfeed less often than adults[7]. In addition, teenage mothers were reported to be less likely to breastfeed than older mothers and have a more rapid discontinuation rate[8,9]. A previous study in Thailand have shown that teenage mothers were significantly less likely to achieve successful breastfeeding at day 2 postpartum compared to adult mothers[10].

Among other factors, nipple length has also been related to successful breastfeeding[11]. Previous studies showed that the rate of successful breastfeeding, measured by LATCH scores, increased with nipple length of ≥ 7 millimeters[11, 12]. Among teenage mothers, it is possible that immature development of breasts and nipples are possibly more common compared to adult mothers. A previous study showed that measurements of nipple-areolar complex were larger among older than younger women[13]. Shorter nipple length among teenage mothers have also been reported among Thai women[10]. The problem of shorter nipple length could further adversely affect the success in breastfeeding among teenagers. However, there is still limited data on the nipple length in teenage mothers as well as their relationship with successful breastfeeding. Therefore, the objectives of this study were to compare nipple characteristics between teenage and adult mothers and to determine the association with success rate of breastfeeding, measured by LATCH scores.

Materials and Methods

An analytic cross-sectional study was conducted between March and October 2016 after approval from the Siriraj institutional review board. The inclusion criteria were singleton, primiparous women who delivered at Siriraj Hospital and agree to participate. Exclusion criteria were women who had contraindications to breastfeeding such as HIV infection. Sample size was determined from pilot study that showed mean nipple length of adult mothers was 9.4 ± 2.8 mm. At 95% confidence level and 80% power with 2:1 control-to-case ratio, and estimated difference of mean nipple length of 1 mm, a total of 105 teenage and 210 adult mothers are required including 10% loss.

After informed consent, a total of 315 postpartum women were enrolled. Study group consisted of 105 teenage mothers and 210 adult mothers were served as a comparison group. Baseline characteristics, obstetric data, and maternal and neonatal outcomes were collected. Nipple length was measured by a plastic syringe with a millimeters scale and nipple width was measured with a round hole's ruler (Fig. 1).

Between 24-48 hours postpartum, each postpartum woman was placed in a sitting position, the nipple was stimulated to an erect state by soft cloth, the nipple length measurement tool was then placed over the nipple, adjusting the inner lip of the tool just to contact the areola and reading the scale (Fig. 2). Nipple width was then measured with a round hole's ruler. Nipple length and width were measured in both breasts and data were recorded

in millimeters.

During admission, all women were advised to exclusive breastfeed their infants. Breastfeeding practice were supported in various aspects individually by well-trained nurses at postpartum ward.

LATCH score was used to determine success in breastfeeding[14]. The scoring system was developed by Jensen et al in 1994 by assessing latching on, audible, type of nipple, comfort, and amount of help the mother needs to hold her infant to the breast. The system assigns a numerical score (0, 1, or 2) for each item. The cut off value for successful breastfeeding was ≥ 7[11,14]. LATCH score of each mother was assessed by a well-trained nurses at day 3 postpartum before hospital discharge.

Comparisons of various characteristics including nipple length and width were made between groups using Student t test or chi square tests as appropriate. Association between nipple characteristics and LATCH score were evaluated. A p value of < 0.05 was considered statistical significance.

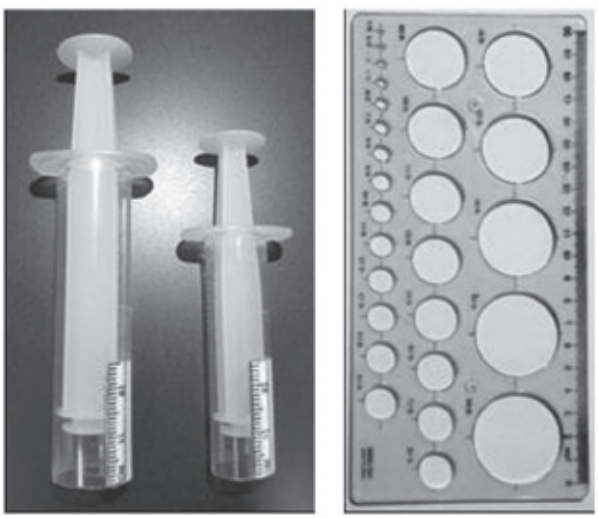

Fig. 1. Plastic syringe with a millimeters scale and round hole's ruler used to measure nipple length and width.

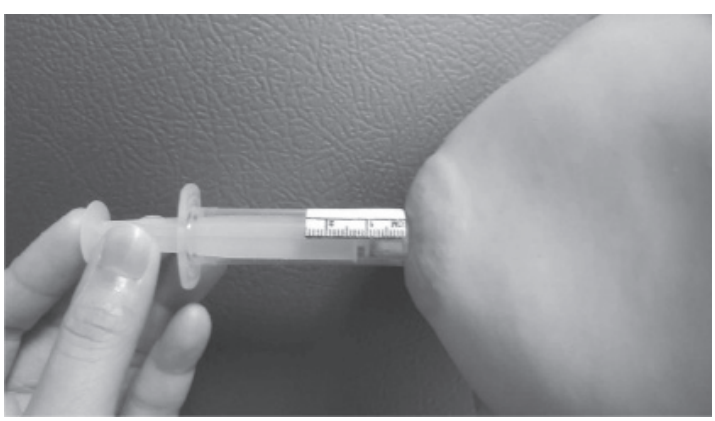

Fig. 2. Measurement of nipple length.

Results

A total of 315 women were enrolled, including 105 teenage and 210 adult mothers. Comparison of various baseline characteristics between the 2 groups are shown in Table 1. Mean age of teenage mothers was 17.5 years while it was 26.8 years in adult mothers ($p < 0.001$) Teenage mothers had significantly lower BMI and more likely to be underweight (37.1% vs. 19.5%, $p < 0.001$). Table 2 shows comparison of delivery characteristics between the 2 groups. Gestational age at delivery were comparable at 38.5 weeks. Teenage mothers were significantly more likely to deliver vaginally than adult mothers (79% vs. 58.6%, $p < 0.001$). Birth weight was significantly lower among teenage than adult mothers (2491.3 vs. 3034 g, $p = 0.045$) but without clinical significance. Newborn sex and rate of birth asphyxia were comparable between the 2 groups.

Table 3 shows comparison of nipple characteristics between the 2 groups. Nipple length and width were significantly lower among teenage compared to adult mothers with the mean nipple lengths of 7.3 ± 2.8 and 9.6 ± 2.8 mm, respectively, $p < 0.001$. Mean nipple width were 13.5 ± 1.4 and 14.2 ± 1.8 mm respectively, $p < 0.001$. Teenage mothers were significantly less likely to have nipple length of ≥ 7 mm compared to adult mothers ($p < 0.001$). Successful breastfeeding as defined by LATCH scores ≥ 7 were comparable between the 2 groups (58.1% vs. 55.2%, $p = 0.631$).

Table 1. Comparison of baseline characteristics between 2 groups.

Characteristics	Teenage (N = 105)	Adult (N = 210)	p value
Mean maternal age ± SD (years)	17.5 ± 1.4	26.8 ± 4.9	< 0.001
Mean BMI ± SD (kg/m^2)	20.3 ± 3.6	22.2 ± 4.6	< 0.001
	N (%)	N (%)	
BMI category			< 0.001
Underweight	39 (37.1%)	41 (19.5%)	
Normal	53 (50.5%)	117 (55.7%)	
Overweight and obesity	13 (12.4%)	52 (24.8%)	
Occupation			< 0.001
Employee	26 (24.8%)	137 (65.2%)	
Housewife	60 (57.1%)	43 (20.5%)	
Others	19 (18.1%)	30 (14.3%)	
Income			< 0.001
≤ 20000 THB	94 (89.5%)	107 (51%)	
> 20000 THB	11 (10.5%)	103 (49%)	

BMI: body mass index, SD: standard deviation

Table 2. Comparison of delivery characteristics between 2 groups.

Characteristics	Teenage (N = 105)	Adult (N = 210)	p value
GA at delivery ± SD (weeks)	38.4 ± 1.5	38.5 ± 1.3	0.75
Route of delivery			< 0.001
Vaginal delivery	83 (79%)	123 (58.6)	
Cesarean delivery	22 (21%)	87 (41.4)	
Newborn sexy			0.72
Male	52 (49.5%)	108 (51.7%)	
Female	53 (50.5%)	101 (48.3%)	
Birth weight ± SD (g)	2941.3 ± 346.6	3034 ± 402.4	0.045
APGAR at 1 min			0.724
< 7	5 (4.8%)	12 (5.7%)	
≥ 7	100 (95.2%)	198 (94.3%)	

GA: gestational age, SD: standard deviation

Table 3. Comparison of nipple characteristics and LATCH score between 2 groups.

Characteristics	Teenage (N = 105)	Adult (N = 210)	p value
Right nipple length ± SD (mm)	7.4 ± 2.9	9.6 ± 3.0	< 0.001
Left nipple length ± SD (mm)	7.2 ± 2.8	9.6 ± 2.9	< 0.001
Mean nipple length ± SD (mm)	7.3 ± 2.8	9.6 ± 2.8	< 0.001
Right nipple length ≥ 7 mm	57 (54.3%)	182 (86.7%)	< 0.001
Left nipple length ≥ 7 mm	59 (56.2%)	180 (85.7%)	< 0.001
Mean nipple length ≥ 7 mm	54 (51.4%)	181 (86.2%)	< 0.001
Any nipple length ≥ 7 mm	62 (59%)	187 (89%)	< 0.001
Right nipple width ± SD (mm)	13.6 ± 1.5	14.2 ± 1.7	< 0.001
Left nipple width ± SD (mm)	13.5 ± 1.4	14.1 ± 2.0	0.009
Mean nipple width ± SD (mm)	13.5 ± 1.4	14.2 ± 1.8	0.002
LATCH score ≥ 7	61 (58.1%)	116 (55.2%)	0.631

SD: standard deviation

Relationship between nipple length and successful breastfeeding at day 3 postpartum is shown in Table 4. For all women, nipple length of ≥ 7 mm significantly increased the success in breastfeeding at postpartum day 3 (63.1% vs. 30.3%, p < 0.001). Similar associations were also observed in both teenage and adult mothers (71% vs. 39.5%, p = 0.001 and 60.4% vs. 13%, p < 0.001, respectively).

Table 4. Relationship between nipple length and LATCH scores.

Characteristics	LATCH score ≥ 7	LATCH score < 7	p value
	All women		
Any nipple length			< 0.001
≥ 7 mm (N=249)	157 (63.1%)	92 (36.9%)	
< 7 mm (N=66)	20 (30.3%)	46 (69.7%)	
	Teenage		
Any nipple length			0.001
≥ 7 mm (N=62)	44 (71%)	18 (29%)	
< 7 mm (N=43)	17 (39.5%)	26 (60.5%)	
	Adult		
Any nipple length			< 0.001
≥ 7 mm (N=187)	113 (60.4%)	74 (39.6%)	
< 7 mm (N=23)	3 (13%)	20 (87%)	

Discussion

Breastfeeding problems are more common in teenage mothers. Maternal age has been reported to be directly associated with the duration of breastfeeding[6]. Many previous studies have demonstrated that teenage mothers were less likely to breastfeed than older mothers and have a more rapid discontinuation rate[7-9]. A previous study in Thailand have shown that teenage mothers were significantly less likely to achieve successful breastfeeding at day 2 postpartum compared to adult mothers[10].

Previous studies showed that nipple length was a strong predictor to determine the successful achievement of breastfeeding at day 3 postpartum. Nipple length of ≥ 7 mm has been reported to facilitate successful breastfeeding[6,7]. The results of this study showed that teenage had significantly shorter nipple length compared to adult mothers. A previous study showed that measurements of nipple-areolar complex were larger among older than younger women but teenage women were not included in such study[13]. Shorter nipple length among teenage mothers have also been reported among Thai women but without statistical significance[10]. There has been no study that specifically aimed to compare nipple characteristics between teenage and adult mothers. In this study, only 59% of teenage mothers had nipple length of ≥ 7 mm compared to 89% among adult mothers. Although there was a report that nipple length and width, and areolar width increase as pregnancy progresses[15], it is possible that maturity of nipple among teenagers is still inadequate in terms of breastfeeding readiness compared to adult mothers.

In terms of successful breastfeeding as assesses by LATCH scores, there was no significant difference between teenage and adult mothers at day 3 postpartum (58.1% vs. 55.2%, p = 0.631). However, further analysis showed that nipple length of ≥ 7 mm

significantly increased breastfeeding success in all mothers, teenage, and adult mothers (63.1% vs. 30.3%, $p < 0.001$; 71% vs. 39.5%, $p = 0.001$; and 60.4% vs. 13%, $p < 0.001$, respectively). This supports that nipple length is an important factor for early success in breastfeeding regardless of age group.

As shorter nipple length was more common in teenage mothers. This issue should be emphasized in clinical practice that all pregnant women should receive breast and nipple examination during antenatal care. Correction of short nipple length should be initiated during pregnancy to better prepare the women for breastfeeding and enhance the success. Women with short nipple should be offered a tool to improve their nipple length. For women with non-protractile nipple, breast shell and Hoffman's exercise have been evaluated for nipple corrections but the results did not showed significant benefits[16,17]. On the other hand, a more recent study showed that breast cup has been evaluated for its success[18]. However, benefits of these tools on short nipple should be further evaluated.

Other factors significantly associated with successful breastfeeding among adolescent mothers included intention to breastfeed, prenatal classes attendance, higher socio-economic status, having spontaneous vaginal delivery, and not having any preexisting health problems or obstetrical complications[6,19]. A previous study reported that only knowledge of the benefits of breastfeeding was not sufficient to result in breastfeeding[8].

Some limitations of this study needs to be addressed. Evaluation for successful breastfeeding by LATCH scores was subjective and the nurses who evaluated the scores were not blinded for mother's age and nipple length. However, LATCH scores evaluation is used routinely in our institution that nurses in postpartum ward are familiar and have experiences in the evaluation. Some of the women in both groups might have some advice on nipple preparation and correction during their antenatal care and could confound the postpartum nipple characteristics. In terms of successful breastfeeding, long-term rates of exclusive breastfeeding were not evaluated and there were other factors related to breastfeeding that might be unmeasurable, such as infant's factors (e.g., suckling), technic (e.g., latching on), psychological factors, social support, knowledge, etc. In addition, there might be limited power in subgroup analysis. Further, large studies are still needed to evaluate the long-term effect of short nipple on breastfeeding. Tools for nipple corrections during antenatal care should also be further evaluated for their benefits.

Conclusion

Teenage had significantly shorter and narrower nipples than adult mothers. Nipple length of ≥ 7 mm was significantly more common among adult than teenage mothers. Pregnant women with nipple length of ≥ 7 mm on at least one side significantly increased the chance of success in breastfeeding at day 3 postpartum regardless of age group.

Potential conflicts of interest

The authors declare no conflict of interest.

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OBSTETRICS

Third Trimester Reference Values of Amniotic Fluid Index in a Group of Healthy Nigerian Women in Jos, Nigeria

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ABSTRACT

Objectives: To ascertain the normal values of amniotic fluid index in third trimester among Nigerian women with uncomplicated singleton pregnancies in Jos, Nigeria.

Materials and Methods: This was a prospective cross-sectional study among 500 healthy pregnant women. Fifty women each were recruited at two-weekly interval from 28-36 weeks' gestation and then weekly up to 41 weeks' gestation. The uterine cavity was divided into four quadrants and using real-time ultrasonography, the vertical diameter of the largest pool of amniotic fluid was measured and summation of the values gave the amniotic fluid index (AFI). Mean, ranges, 5th, 10th, 50th, 90th and 95th percentiles for each gestational age were calculated using SPSS version 20 (IBM, Armonk, NY, USA).

Results: Mean AFI among the entire study population was 18.1±3.1 cm (range of 10.4-26.8 cm) while the mean AFI for preterm and term pregnancies were 18.5±2.6 cm and 17.8±3.5 cm respectively. The AFI reference range for the study population was 13.6-24.6 cm. Amniotic fluid volume was highest at 28 weeks, stabilized and plateau between 37-39 weeks and declined after 40 weeks' gestation. Using 5th and 95th percentile as lower and upper limits of normal, reference ranges for each gestational age was ascertained.

Conclusion: Third trimester reference ranges of AFI is established and this can be used as a guide for evaluation of amniotic fluid volume in this obstetric population.

Keywords: amniotic fluid index, pregnancy, reference ranges, Nigeria

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Introduction

Antepartum fetal surveillance with the aim of detecting fetuses that are in distress or compromised by adverse obstetric factors so as to effect timely delivery is essential in preventing or reducing perinatal morbidity and mortality[1,2]. Assessment of amniotic fluid volume is an important component of modified biophysical profile, a useful method for assessment of fetal wellbeing[2,3]. Amniotic fluid surrounds the fetus throughout pregnancy providing nutrition, supporting and helping in the development of fetal lungs. Its volume is an important indicator of in-utero fetal wellbeing and this makes its quantification an important means of antenatal fetal assessment[4,5]. Amniotic fluid volume is largely determined by balance between fetal urine production and fluid resorption through fetal swallowing in the third trimester[2,4].

Variations in amniotic fluid volumes may be a reflection of fetal compromise and are predictive of perinatal morbidity and mortality[1,4]. Extreme changes in amniotic volumes are often associated with poor pregnancy outcomes[1,2]. Some maternal and fetal medical conditions including diabetes mellitus, hypertensive disorders in pregnancy, placental insufficiency, intra-uterine growth restriction and fetal renal and gastro-intestinal anomalies[5-7] are associated with abnormalities in amniotic fluid volumes. Different methods are used for the assessment of amniotic fluid volume including palpation, amniocentesis with dye dilution and ultrasonography[7-9]. Ultrasound assessment of amniotic fluid especially changes in its volumes is an essential and integral component of pregnancy assessment in modern obstetric practice[4,7].

This study was undertaken to establish the normal reference ranges of amniotic fluid volume in third trimester among a group of Nigerian women with uncomplicated singleton pregnancies because of the importance of amniotic fluid to the fetus and its volume as a marker of fetal wellbeing. This will enhance the detection of abnormalities in amniotic fluid volumes among high risk pregnancies leading to timely interventions and thereby saving the fetuses from intra-uterine death.

Materials and Methods

This was a prospective cross-sectional study of amniotic fluid volumes among 500 healthy pregnant women with singleton pregnancy between 28-41 weeks of gestation attending antenatal care at the Bingham University Teaching hospital, Jos between January and December 2017. Fifty pregnant women each were recruited consecutively at 2-weekly intervals at 28, 30, 32, 34, and 36 weeks' gestation and then weekly at term from 37, 38, 39, 40 and 41 weeks of gestation. Consent was obtained verbally. Inclusion criteria included consenting women with low risk pregnancy and reliable last menstrual period with dates correlating with ultrasound estimated gestational age done within the first half of pregnancy. Women with hypertensive disorders in pregnancy, pre-gestational or gestational diabetes mellitus, intrauterine growth restriction, fetal congenital abnormalities, preterm births as well as those with other medical or obstetric conditions were excluded from the study. Women at 42 weeks of gestation were also not included as we routinely induce labor for pregnancy beyond 41 weeks in our centre.

The amniotic fluid index of recruited women grouped according to gestational ages was assessed using portable Mindray(R) DP-2200 (Shenzhen Mindray Bio-medical Electronics Co Ltd, China 2010) ultrasound machine with a Curvilinear 3.5 MHz transducer. Each subject was scanned in supine position by the same sonographer to reduce inter-observer error using the method describes by Phelan et al[10]. The uterus was arbitrarily divided into for quadrants using the linea nigra as a vertical line and a transverse line at the level of the umbilicus. In each of these quadrants, the transducer was placed in sagittal plane perpendicular to patient's abdomen and maximum vertical depth of amniotic fluid was measured in centimeters after excluding presence of fetal parts or loops of

umbilical cord. The summation of the values from the four quadrants gave the amniotic fluid index (AFI).

Data was entered into and analyzed descriptively to ascertain the mean, standard deviation, and percentile values of AFI for each group at the various gestational age using SPSS version 20 (IBM, Armonk, NY, USA). Percentile values (5th, 50th and 95th) were plotted using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) for the selected gestational ages. Ethical clearance for the study was granted by the Human Research and Ethics Committee of Bingham University Teaching Hospital, Jos.

Results

The mean age of the recruited women was 30.6 ±5.4 years with a range of 22-41 years. Ten percent of the women were primigravidae, 76.0% and 13.0% were of gravidity 2-4 and ≥ 5 respectively. Majority of the women (73.3%) were multiparous while 16.7% and 10.0% were primiparous and nulliparous respectively.

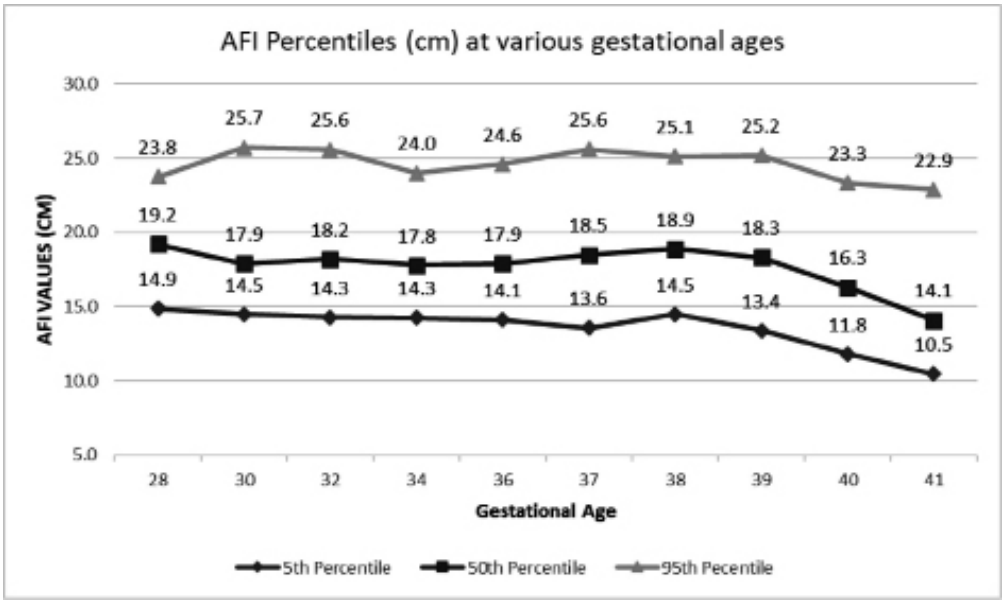
The mean late trimester AFI among the study population was 18.1±3.1 cm with a range of 10.4-26.8 cm. The mean AFI for preterm and term pregnancies were 18.5 ± 2.6 cm and 17.8 ± 3.5 cm respectively. The overall average normal range of AFI among the study population was 13.6-24.6 cm when the 5th and 95th percentiles were used as lower and upper limits respectively. Table 1 depicts the descriptive statistics of the AFI among the women. The 5th, 50th, and 95th percentiles ranged from 14.9, 19.2 and 23.8 cm respectively at 28 weeks gestation to 10.5, 14.1 and 22.9 cm respectively at 41 weeks gestation.

The trend of AFI in the study population showed that amniotic fluid volume was highest at 28 weeks of gestation and later stabilized and plateau between 37-39 weeks of gestation. Thereafter, there was decline in volumes with lowest volume noted at 41 weeks' gestation (Table 1). Between 28 and 40 weeks of gestation (12 weeks period), there was 10.4% decrease in mean AFI while the decline between 40 and 41 weeks (one week interval) of gestation was 8.7%. Fig 1 shows the pattern of decline in AFI with increasing gestational age. Table 2 shows the reference ranges (5th and 95th percentiles as lower and upper values respectively) of amniotic fluid index in late trimester in the study population.

Table 1. AFI parameters (cm) at various gestational ages; mean, standard deviation, percentile values.

Gestational age (weeks)	Mean	Standard deviation	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
28	19.3	2.4	14.9	15.9	19.2	22.6	23.8
30	18.5	2.8	14.5	14.9	17.9	22.0	25.7
32	18.9	3.1	14.3	14.8	18.2	24.4	25.6
34	17.9	2.6	14.3	14.9	17.8	22.3	24.0
36	17.9	2.3	14.1	14.5	17.7	21.6	24.6
37	18.8	3.4	13.6	14.4	18.5	24.1	25.6
38	18.4	3.1	14.5	15.2	18.9	24.3	25.1
39	18.6	3.6	13.4	14.2	18.3	24.2	25.2
40	17.3	3.4	11.8	13.0	16.3	22.2	23.3
41	15.8	3.8	10.5	10.6	14.1	21.5	22.9

AFI: amniotic fluid index



AFI: amniotic fluid index

Fig. 1. Graphical representation of AFI (cm) at 5th, 50th and 95th percentiles at various gestational ages.

Table 2. Reference ranges of AFI at various gestational ages among the study population.

Gestational age (weeks)	Reference Ranges (cm)	
	Lower range	Upper range
28	14.9	23.8
30	14.5	25.7
32	14.3	25.6
34	14.3	24.0
36	14.1	24.6
37	13.6	25.6
38	14.5	25.1
39	13.4	25.2
40	11.8	23.3
41	10.5	22.9

AFI: amniotic fluid index

Discussion

Assessment of amniotic fluid volume is a very important modality for ascertaining fetal wellbeing. Hence the need to establish the normal values in any obstetric population as its abnormalities are associated with adverse pregnancy outcomes. The mean AFI among our subjects was 18.1±3.1 cm with a range of 10.4-26.8 cm. This was slightly greater than mean values of 14.07±3.34 cm and 13.85±3.61 cm reported among pregnant women in Northeastern Thailand and

Southern Nigeria respectively[12,15]. This may be attributed to differences in obstetric populations, methodology and different gestational ages the women were recruited for the study as other researchers included women from 20 weeks of gestation in their studies. In our study, the mean AFI of 19.3 cm at 28 weeks gestation was highest, remain relatively stable up to 40 weeks gestation and then dropped to 15.8 cm at 41 weeks' gestation. However, there was no appreciable difference between the mean AFI for preterm and term gestations among our subjects. This trend in amniotic fluid volume among healthy pregnant women was also noted by other researchers elsewhere[6,12,13,15,16]. These similar trends are probably a reflection of normal physiological changes in amniotic fluid volumes in pregnant women irrespective of obstetric population, race and geographical location. Also, the physiological fall in amniotic fluid volume after 40 weeks' gestation as noted also in this study was probably ascribed to gradual reduction in fetal urine production as a result of decreasing fetal growth and placental function[17]. This trend was also noted among different obstetric populations by other researchers[6,10,12,15].

Comparing the 50th percentile in this study with previous figures reported from different regions and ethnic groups, our values were higher compared to values reported from Iranian, Thai, Nigerian (Igbo ethnic group) and Chinese obstetric populations[11-14] (Table 3). These findings suggested that racial and environmental factors may influence amniotic volume among pregnant women. Different normal ranges of AFI among healthy pregnant women have been reported by many researchers but reference values of 5.0-25.0 cm reported by Moore and Cayle as well as Magann EF et al have been widely used suggesting values < 5.0 cm and > 25.0 cm as oligohydramnios and polyhydramnios respectively[9,18]. The overall normal range of AFI among our subjects was 13.6- 24.6 cm when 5th and 95th percentiles are used as lower and upper limits of normal. Hence, values indicating oligohydramnios and polyhydramnios in our study were different from other studies[9, 12, 19 – 21]. This is a reflection of the fact that there are wide variations in reference standards for AFI in different obstetric populations, race and geographical locations. Establishment of normal reference values of AFI for a particular obstetric population cannot be over-emphasized as abnormalities in amniotic fluid volume especially oligohydramnios are associated with higher rate of caesarean deliveries due to fetal distress, meconium aspiration and poor perinatal outcomes[1,2,22,23].

Table 3. Comparison of 50th percentile of the AFI with others from different ethnic groups.

Gestational age (weeks)	Present Study 2018	Birang SH 2008[11]	Samakeenit B, et al 2015[12]	Agwu EJ, et al 2016[13]	Mongelli M, et al 1999[14]
28	19.2	14.5	14.3	15.4	13.6
30	17.9	14.5	13.9	15.2	13.9
32	18.2	14.3	12.7	12.8	13.9
34	17.8	14.0	14.9	12.7	13.6
36	17.7	12.9	12.9	12.4	13.1
37	18.5	13.0	12.0	11.7	12.7
38	18.9	13.0	11.9	11.6	12.2
39	18.3	12.9	10.9	11.4	--
40	16.3	12.7	11.7	10.6	---
41	14.1	11.1	-	10.4	-----

AFI: amniotic fluid index

Also from our results, there was appreciable decline in amniotic fluid index after 40 weeks of gestation (5th percentile was 10.5 cm at 41 weeks' gestation) compared to degrees of changes in AFI between earlier gestational ages. This remarkable change in AFI at 41 weeks of gestation was also noted by other researchers[11,12,21,24,25]. This suggests that the need for delivery of the fetus after 41 weeks' gestation is essential among our study population to reduce the risk of perinatal morbidity and mortality.

Limitations of this study included its cross-sectional nature instead of a longitudinal design as well as non-consideration of possible confounding variables such as maternal obesity in the study. Another limitation of the study was non recruitment of subjects at 29, 31, 33, and 35 weeks as the study was set out to determine AFI at even numbers gestational ages before term. However, the strengths of the study included its prospective nature and ultrasonograhic scanning by the same sonographer thereby avoiding inter-observer bias.

Conclusion

The normal reference values for AFI in this obstetric population are established and can be used as a guide for the diagnosis of oligohydramnios and polyhydramnios. Large multicentre study across different regions in Nigeria is recommended to estimate more accurate AFI reference values among pregnant Nigerian women.

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Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Lidocaine Spray for Pain Control during Office-based Endometrial Biopsy: A randomized placebo-controlled trial

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ABSTRACT

Objectives: To evaluate effectiveness of 10% lidocaine spray for pain relief during office-based endometrial biopsy

Materials and Methods: Fifty women who indicated for endometrial tissue sampling by Wallach endocell® participated in this randomized, double blinded, placebo-controlled study. The procedures were performed at out-patient gynecology clinic, Department of Obstetrics and Gynecology, Vajira hospital, Bangkok, Thailand, from July 2016 to April 2017. Participants were simple randomly assigned to either lidocaine group which they will receive 5 puff of 10% lidocaine solution spray (50 mg), four puff to cervical surface and one puff towards internal os, or placebo group which they will receive 5 ml placebo solution spray administered in the same manner. Pain score was measured intraoperation, immediate after, 15 minutes and 30 minutes post-operation, using a 10 cm-visual analog scale (VAS-10).

Results: Lidocaine spray application during office-based endometrial biopsy significantly lowered the overall pain score compared with placebo (coefficient -3.27, $p < 0.001$, multilevel linear regression). Mean pain score during procedure was 3.56 ± 1.50 in the lidocaine group (n=25) and 7.28 ± 1.02 in the placebo group (n=25) ($p < 0.001$). The mean pain score immediate after, at 15 and 30 minutes after the procedure was 3.04 ± 1.31, 0.80 ± 1.41 and 0.08 ± 0.40 in the lidocaine spray group respectively and 7.08 ± 1.19, 3.92 ± 1.47 and 1.92 ± 1.41 in the placebo group respectively ($p < 0.001$).

Conclusion: 10% lidocaine spray applied at cervical surface and internal cervical os was effective for pain relief during and immediate after office-based endometrial Biopsy.

Keywords: endometrial biopsy, lidocaine spray, pain control, analgesia

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การใช้ Lidocaine spray ในการระงับอาการปวดระหว่างการดูดเนื้อเยื่อบุโพรงมดลูกที่ห้องตรวจผู้ป่วยนอก: การทดลองแบบสุ่มและมีกลุ่มควบคุม

ปวีร์ กอสุวรรณ, บุษบา วิริยะสิริเวช์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการพ่น 10% Lidocaine spray เพื่อลดความเจ็บปวดขณะเก็บดูดชิ้นเนื้อเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *สตรีที่มีข้อบ่งชี้ในการเก็บชิ้นเนื้อโพรงมดลูกจำนวน 50 ราย ที่มารับการตรวจที่ห้องตรวจผู้ป่วยนอก ภาควิชาสูตินรีเวช คณะแพทยศาสตร์วชิรพยาบาล เข้าร่วมการศึกษา โดยใช้อุปกรณ์ Wallach Endocell® เก็บตรวจชิ้นเนื้อโพรงมดลูก ทำการสุ่มโดยแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยา 10% Lidocaine spray และกลุ่ม Placebo พ่นก่อนทำหัตถการทั้งหมด 5 puff โดย 4 puff ที่ บริเวณผิวปากมดลูก และ 1 puff ที่บริเวณปากมดลูกด้านใน ทำการวัดระดับความเจ็บปวดโดยใช้ 10 cm-visual analog scale (VAS-10) ขณะทำหัตถการเก็บดูดชิ้นเนื้อโพรงมดลูก, หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที ตามลำดับ*

ผลการศึกษา: *กลุ่มที่ได้รับ 10% Lidocaine spray พบค่าเฉลี่ยความเจ็บปวดต่ำกว่ากลุ่มที่ได้รับ Placebo อย่างมีนัยสำคัญทางสถิติ ทั้งขณะทำหัตถการเก็บดูดชิ้นเนื้อโพรงมดลูก, หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที โดยค่าเฉลี่ยความเจ็บปวด 3.56 ± 1.50 ในกลุ่มที่ได้รับ 10% Lidocaine spray (n=25) และ 7.28 ± 1.20 ในกลุ่ม Placebo (n = 25) ($p < 0.001$). ค่าเฉลี่ยความเจ็บปวดในกลุ่ม 10% Lidocaine หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที คือ 3.04 ± 1.31, 0.80 ± 1.41, 0.08 ± 0.40 ตามลำดับ และค่าเฉลี่ยความเจ็บปวดในกลุ่ม Placebo คือ 7.08 ± 1.19, 3.92 ± 1.47, 1.92 ± 1.41 ตามลำดับ*

สรุป: *การพ่น 10% Lidocaine spray ที่บริเวณผิวปากมดลูก และปากมดลูกด้านใน มีประสิทธิภาพในการลดอาการปวดระหว่างการดูดชิ้นเนื้อเยื่อบุโพรงมดลูกจนถึงหลังทำหัตถการ 30 นาที*

คำสำคัญ: *เก็บชิ้นเนื้อเยื่อบุโพรงมดลูก, ลิโดเคนสเปรย์, ลดอาการเจ็บปวด, ยาระงับความเจ็บปวด*

Introduction

An endometrial biopsy (EB) is a common medical procedure for the investigation of many gynecological disorders including abnormal premenopausal and postmenopausal uterine bleeding, abnormal cytology, hormonal therapy failure, and infertility[1,2]. Over the years, office-based EB has increasingly replaced dilatation and curettage (D&C) as the standard pathological examination method of the endometrium as EB is a simple, quick, safe, and inexpensive treatment that does not require anesthesia[3]. Several disposable endometrial suction devices can be used for EB including Wallach's Endocell®, Pipelle, Vabra aspiration, Z-sampler, Accurette, Explora, and Karman systems. Wallach's Endocell® is usually used as this technique is simple, quick, less painful, and provides adequate tissue for histological examination[4]. There is no standard guideline for pain control during an EB procedure which is usually performed without any analgesia. However, recent studies found that all patients experienced pain during outpatient EB procedure, and two-thirds had moderate to severe pain that prevented collection of adequate tissue sample for biopsy[3]. Techniques proposed for pain management during EB include paracervical block, intrauterine lidocaine infusion, non-steroidal anti-inflammatory drugs (NSAIDs) and the local application of lidocaine spray as a topical anesthetic agent available in 10% form which contains 10 mg of lidocaine per puff. A long applicator is convenient for administration. Recommended dosage is 40-50 mg for an obstetrics and gynecological procedure. Onset of analgesia occurs after 1-2 minutes with duration of action at 15-30 minutes which is adequate for the EB procedure[5,6]. However, previous studies concerning the efficacy of lidocaine for pain control during office-based EB are inconclusive[7-12].

Hence, this randomized, double-blinded, placebo-controlled trial evaluated the effectiveness of 10% lidocaine spray on reducing pain perception during office-based EB.

Materials and Methods

This study was performed at the Department of Obstetrics and Gynecology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand from July 2016 to April 2017. This study was approved by the Vajira Institutional Review Board (VIRB), Faculty of Medicine, Vajira Hospital, Bangkok, Thailand and registered at http://www.thaiclinicaltrials.gov (TCTR20170714001) according to the standards set by the International Committee of Medical Journal Editors and the World Health Organization. Sample size was calculated using the estimated difference in pain score between lidocaine and placebo groups determined by Aksoy H et al[8]. With power of 80%, a type I error of 0.05 and a two-sided test sample gave the size of each group as 22. Adding 10% drop out, this was increased to 25. Inclusion criteria were age ≥ 18 years, showing indication for office-based EB, no previous allergic reaction or sensitivity to lidocaine and a written consent form. Exclusion criteria were currently pregnant, had cervical pathology, uterine anomaly, untreated acute cervicitis or pelvic inflammatory disease, inability to determine 10-cm visual analog scale (VAS-10) pain score, received medication such as analgesics and misoprostol prior to operation, had respiratory tract problems, cardiovascular system failure, acute liver disease, or active bleeding from the vagina on the date of operation[15]. A total of 50 women met the eligibility criteria. After receiving adequate study information, written informed consent was obtained from all participants prior to enrollment.

Randomization was performed using a computer-generated random number chart. The randomization order was blinded to the physician who performed the EB, participants, and research assistants who assessed the pain score. Ten percent lidocaine (10% Xylocaine spray®, 10 mg/ 1 ml/ 1 puff, AstraZeneca) and placebo (isotonic saline solution) were prepared by the pharmacist with identical appearance. The suction device used was a Wallach Endocell®, a flexible plastic catheter with

manual suction of diameter 3.1 mm. A pain measurement scale calibrated from zero to ten was used to assess pain score with "0" indicating "Null pain" and "10" indicating highest pain intensity. Participants were randomly assigned to 2 groups (lidocaine and placebo). The lidocaine group A received 5 puffs of 10% lidocaine solution spray, 4 puffs to the cervical surface and 1 puff toward the internal cervical os for 2 cm. A long applicator was convenient for administration. Group B received 5 ml placebo solution spray administered in the same manner. The EB was performed by the same gynecologist to maintain consistency as per the following steps: the participant was placed in the lithotomy position and a sterile bivalve speculum was introduced into the vagina to visualize the cervix, the cervix and vagina were cleaned with 10% povidone-iodine solution, each participant received 5 puffs of either 10% lidocaine solution spray or placebo and waited for 2 minutes for the analgesic to take effect. The EB was performed by passing a Wallach Endocell® into the uterine cavity. Once in position, the plunger was drawn back to create suction and the device was moved gently from the fundus down to the internal os until it was filled with tissue. If required, a tenaculum was used to grasp the anterior cervix and straighten the uterine axis, and EB was performed as standard manner. Bleeding was checked and the speculum was withdrawn. Participants were observed for 30 minutes after the procedure. Pain intensity was assessed by a research assistant at 5 different time points: speculum introduction which was considered as baseline pain, during biopsy and then immediately, 15 minutes, and 30 minutes after the biopsy. Participants' demographics and medical data including age, body mass index, gravidity, parity, previous vaginal delivery, menopause status, medical history, indication for biopsy, uterine size, length, position and uterine pathology, pain score at each time point, complications from the procedure such as vasovagal reactions, and adverse reaction from the lidocaine were collected.

Data were analyzed using Stata/SE 13 statistical software. Continuous variables were presented as descriptive statistics (mean ± standard deviation) and analyzed by Student's t-tests. Multilevel linear regression was used to compare the difference of overall pain score between the lidocaine and placebo groups. A p value < 0.05 was considered to be statistically significant.

Results

A total of 50 women who met the eligibility criteria were enrolled from 58 candidates (86.21%, Fig. 1). Eight patients refused to participate and were excluded. All procedures were successfully completed without any complications, and no serious adverse reactions associated with Lidocaine were noted. Participants were equally randomized into Lidocaine and placebo groups. Demographic and clinical characteristics of the patients were similar in each group (Table 1), regression was used to compare the difference of overall pain score between the Lidocaine and placebo groups. A $p<0.05$ was considered to be statistically significant.

No statistically significant differences were recorded in mean pain score at the time of speculum insertion, considered as baseline pain, between Lidocaine (3.24 ± 1.58) and the placebo group (2.58 ± 1.79) ($p = 0.21$, Table 2). Lidocaine spray application significantly lowered overall pain score of the EB procedure compared with placebo (coefficient -3.27, $p < 0.001$, multilevel linear regression). Mean pain score during the procedure was 3.56 ± 1.50 in the Lidocaine group ($n = 25$) and 7.25 ± 1.03 in the placebo group ($n = 24$) ($p < 0.001$). Mean pain scores immediately after and at 15 and 30 minutes after the procedure were 3.04 ± 1.30, 0.80 ± 1.41 and 0.08 ± 0.40 in the Lidocaine spray group and 7.04 ± 1.03, 3.88 ± 1.48 and 1.92 ± 1.44 in the placebo group, respectively ($p < 0.001$). Significant differences between the two groups regarding pain intensity are shown in Table 1. Fig. 2. elucidates the subgroup analyses performed for groups where a tenaculum was or was not used. Results indicated that Lidocaine was significantly effective in

reducing pain whether or not a tenaculum was used (Fig. 2. and 3.).

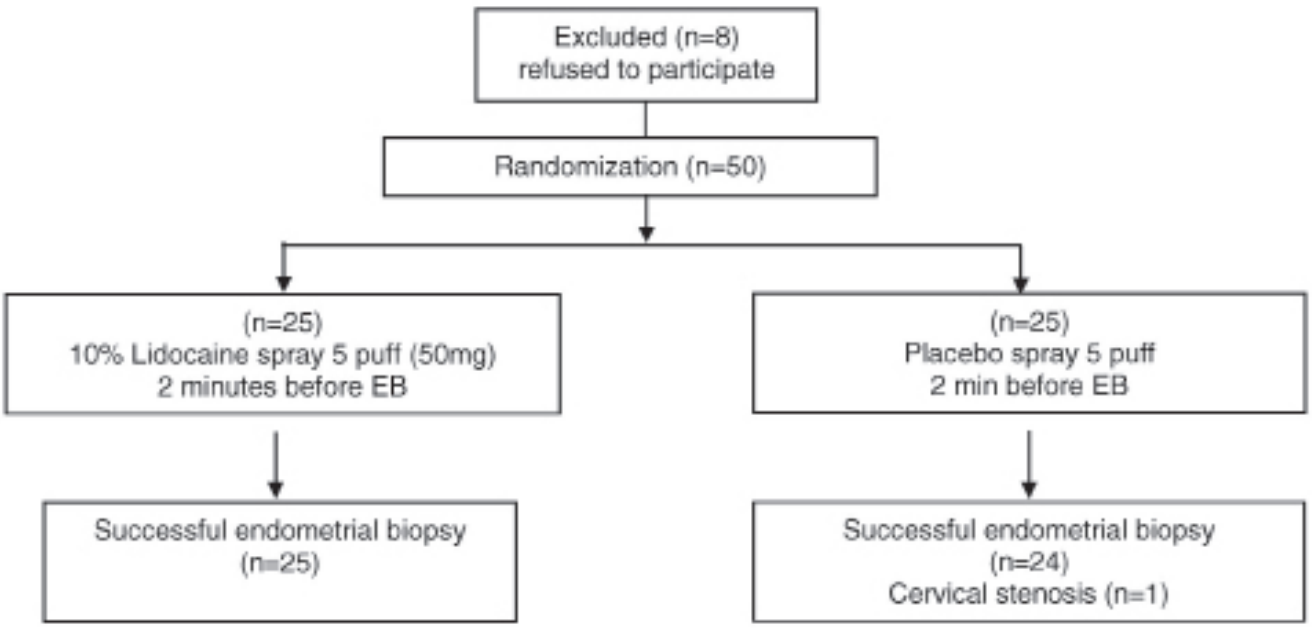
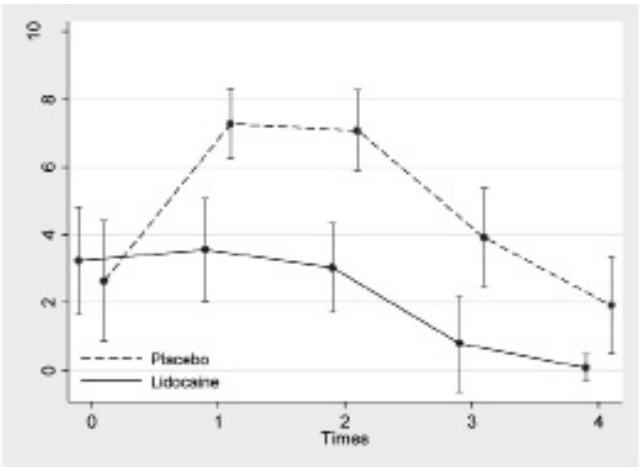


Fig. 1. Flow chart showing progression of participants through trial.

Table 1. Demographic and clinical characteristics of the study groups.

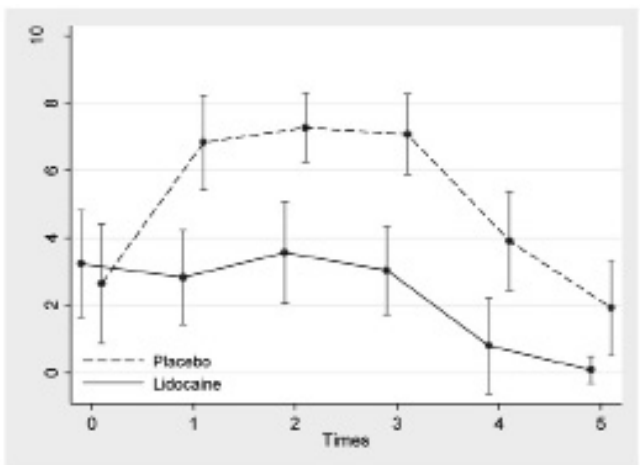
	Lidocaine group (n=25)	**Placebo (n=25)**
Age (year)* (mean ± SD)	51.5 ± 10.6	49.6 ± 11.3
BMI (mean ± SD)	25.6 ± 3.1	26.1 ± 6.2
Previous vg delivery n (%)	19 (76)	17 (68)
Menopausal status' n (%)		
Premenopausal	18 (72)	17 (68)
Post-menopausal	7 (28)	8 (32)
Indication n (%)		
abnormal uterine bleeding	18 (72)	14 (56)
postmenopausal bleeding	7 (28)	8 (32)
endometrial dating	0 (0)	3 (12)
Tenaculum used	11 (44)	12 (48)

Values are expressed as n (%) unless otherwise specified.



Time
0 = At the time of introduce speculum
1 = During endometrial biopsy
2 = Immediately after endometrial biopsy
3 = 15 min after endometrial biopsy
4 = 30 min after endometrial biopsy

Fig. 2. Mean pain score in each group within the course of study.



Time
0 = At the time of introduce speculum
1 = During endometrial biopsy
2 = Immediately after endometrial biopsy
3 = 15 min after endometrial biopsy
4 = 30 min after endometrial biopsy

Fig. 3. Mean pain score in each group when Tenaculum were used.

Table 2. Mean pain score at five time point of study groups.

	Lidocaine group (n=25)	Placebo (n=25)	p value
VAS speculum (cm)	3.24 ± 1.58	2.58 ± 1.79	0.21
VAS intra-op (cm)	3.56 ± 1.50	7.28 ± 1.02	< 0.001
VAS immediate post-op (cm)	3.04 ± 1.31	7.08 ± 1.19	< 0.001
VAS postop 15 min (cm)	0.8 ± 1.41	3.92 ± 1.47	< 0.001
VAS post op 30 min (cm)	0.08 ± 0.4	1.92 ± 1.46	< 0.001

Values are expressed as n (%) unless otherwise specified.

Discussion

Assessment of the endometrium is required in many gynecological examinations and an endometrial biopsy is a common outpatient procedure for detection of endometrial pathology. Screening for cancer or precancerous conditions can determine the cause of abnormal uterine bleeding, fertility problems and response to hormonal treatment[2,3]. An endometrial biopsy allows the collection of tissue from the cervix and the uterus for histological evaluation but the procedure may be painful. The cervix and uterus are richly innervated and pain perception results from two distinct neural pathways as the Frankenhäuser plexus (parasympathetic nerves S2-4) supplying the cervix and lower uterus, and sympathetic nerves passing via the infundibulopelvic ligament from the ovarian plexus supplying the uterine fundus[13,14]. Pain and discomfort are associated with the transcervical insertion of an endometrium suction device and a tenaculum used for uterine traction. Currently, there are many treatment options but pain management for the successful completion of procedures is inconclusive. Previous studies indicated pain scores ranging from 5-7 on the 10-cm VAS scale12 while Paphada et al., 2013 reported that 60% of patients experienced moderate to severe pain during the procedure[4].

Lidocaine spray is a simple and convenient topical anesthetic agent with no pain related to application and rapid onset of action at 1-2 minutes with 15-30 minute duration. The mechanism of local lidocaine can block pain at the Frankenhäuser plexus[12]. Previous authors showed that lidocaine spray is effective in reducing pain during minor gynecological procedures[16,17], with positive effects during Pipelle endometrial aspiration; however, these results were inconsistent with other studies which examined the potential role of topical anesthetics for pain control during endometrial biopsy. Results in Table 1. and Fig. 1. showed that lidocaine spray can reduce pain during and immediately after the procedure, and was effective for up to 30 minutes.

Our study was a randomized, double-blinded, placebo-controlled trial. One limitation was the use of a Wallach Endocell® diameter 3.1 mm; other types of suction devices with larger diameters may require different dosages of analgesia.

Conclusion

Ten percent lidocaine spray was an effective option for pain management during office-based EB. Gynecologists should, therefore, consider using this spray in routine practice.

Potential conflicts of interest

The authors declare no conflict of interest.

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GYNECOLOGY

Prognostic Factors and Survival Rates in Early-stage Cervical Cancer Patients Treated with Radical Hysterectomy and Pelvic Lymphadenectomy

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ABSTRACT

Objectives: To evaluate prognostic factors and survival rates in early-stage cervical cancer patients who had been treated with radical hysterectomy and pelvic lymphadenectomy (RHPL).

Materials and Methods: Medical records and pathologic findings of 177 cervical cancer patients who had International Federation of Gynecology and Obstetrics (FIGO) stage IA2-IIA and underwent RHPL at Buddhachinaraj Phitsanulok Hospital from January 2005 to December 2016 were retrospectively reviewed. Clinicopathologic variables and treatment data were collected.

Results: Among 177 patients, mean age was 49.9 ± 11.0 years. The median follow-up time was 42 months. Twenty-five patients had a recurrence and 7 patients died from disease. A five-year disease free survival (DFS) rate and a 5-year cancer-specific survival (CSS) rate were 89% and 96.6%, respectively. The independent prognostic factors for DFS were increasing age and pelvic lymph node metastasis (hazard ratio [HR] 1.06; 95%CI 1.02-1.10, and HR 4.63; 95%CI 1.21-17.64, respectively). No significant differences in FIGO stage, histology, positive surgical margin, parametrial involvement, pelvic lymph node metastasis, deep stromal invasion, lymph vascular space invasion, and tumor size were identified as independent prognostic factors for CSS. However, adenocarcinoma (AC) patients with parametrial involvement, pelvic lymph node metastasis, and postoperative treatment followed by concurrent chemoradiotherapy (CCRT) had a significantly worse survival outcome than those with squamous cell carcinoma (SCC) (HR 11.87; 95%CI 1.46-46.20, HR 7.00; 95%CI 1.55-31.66, and HR 7.20; 95%CI 1.57-32.85, respectively).

Conclusion: Early-stage cervical cancer patients who underwent RHPL showed good survival rates. The independent prognostic factors for DFS were increasing age and pelvic lymph node metastasis whereas no prognostic factors for CSS were found. Furthermore, parametrial involvement, pelvic lymph node metastasis, and postoperative treatment followed by CCRT were likely to be predictors for poorer survival outcomes in AC than those in SCC.

Keywords: cervical cancer, prognostic factor, survival, radical hysterectomy

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ปัจจัยพยากรณ์โรคและอัตราการรอดชีวิตของผู้ป่วยมะเร็งปากมดลูกระยะแรกที่รักษาโดยการตัดมดลูกออกแบบถอนรากถอนโคนร่วมกับการเลาะต่อมน้ำเหลืองในอุ้งเชิงกราน

พลอยไพลิน ธนาภินันท์, บุญชัย นาคอริยกุล, พรสวรรค์ วาสิงหนท์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาปัจจัยพยากรณ์โรค และอัตราการรอดชีวิตในผู้ป่วยมะเร็งปากมดลูกระยะแรก ที่รักษาโดยการตัดมดลูกออกแบบถอนรากถอนโคน และเลาะต่อมน้ำเหลืองในอุ้งเชิงกราน*

วัสดุและวิธีการ: *การศึกษาย้อนหลังโดยการทบทวนเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกระยะ IA2-IIA ที่รักษาโดยการตัดมดลูกออกแบบถอนรากถอนโคน จำนวน 177 คน ในโรงพยาบาลพุทธชินราช พิษณุโลก ในช่วงระยะเวลาตั้งแต่มกราคม พ.ศ.2548 ถึง ธันวาคม พ.ศ.2559 โดยเก็บข้อมูลทางคลินิก ผลพยาธิวิทยา และการรักษา*

ผลการศึกษา: *ในผู้ป่วยมะเร็งปากมดลูกจำนวน 177 คน มีค่าอายุเฉลี่ยเท่ากับ 49.9 ± 11.0 ปี ค่ามัธยฐานของช่วงเวลาในการติดตามการรักษาเท่ากับ 42 เดือน มีผู้ป่วยจำนวน 25 คน เกิดการกลับเป็นซ้ำของโรค และ 7 คน เสียชีวิตจากมะเร็งปากมดลูก อัตราการกลับเป็นซ้ำของโรคและอัตราการรอดชีวิตที่ 5 ปี เท่ากับร้อยละ 89 และ 96.6 ตามลำดับ ปัจจัยพยากรณ์โรคที่มีผลต่อการกลับเป็นซ้ำของโรค คือ อายุที่เพิ่มขึ้น และการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองในอุ้งเชิงกราน นอกจากนี้ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของระยะโรค ชนิดพยาธิวิทยา การตรวจพบรอยโรคที่ขอบของชิ้นเนื้อ การลุกลามพารามีเทรียม การแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองในอุ้งเชิงกราน การลุกลามสโตรมาชั้นลึก การลุกลามหลอดเลือดหรือหลอดน้ำเหลือง และขนาดของก้อนมะเร็งใหญ่กว่า 4 เซนติเมตร ที่เป็นปัจจัยพยากรณ์โรคที่มีผลต่ออัตราการรอดชีวิต อย่างไรก็ตาม พบว่าพยาธิวิทยาชนิด adenocarcinoma (AC) ที่มีการลุกลามพารามีเทรียม การแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองในอุ้งเชิงกราน และการรักษาหลังผ่าตัดโดยการให้เคมีบำบัดและฉายแสงร่วมด้วย มีพยากรณ์โรคของการรอดชีวิตแย่กว่าชนิด squamous cell carcinoma (SCC) อย่างมีนัยสำคัญทางสถิติ*

สรุป: *ผู้ป่วยมะเร็งปากมดลูกระยะแรกที่รักษาโดยการตัดมดลูกออกแบบถอนรากถอนโคน และเลาะต่อมน้ำเหลืองในอุ้งเชิงกรานมีอัตรารอดชีวิตที่สูง ปัจจัยพยากรณ์โรคสำคัญต่อการกลับเป็นซ้ำของโรคคือ อายุที่เพิ่มขึ้นและการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองในอุ้งเชิงกราน แต่ไม่พบปัจจัยพยากรณ์โรคที่มีผลต่ออัตราการรอดชีวิต นอกจากนี้การลุกลามพารามีเทรียม การแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองในอุ้งเชิงกราน และการรักษาหลังผ่าตัดโดยการให้เคมีบำบัด และฉายแสงเป็นปัจจัยที่ทำให้อัตราการรอดชีวิตในชนิด AC แย่กว่าเมื่อเปรียบเทียบกับชนิด SCC*

คำสำคัญ: *มะเร็งปากมดลูก, ปัจจัยพยากรณ์โรค, อัตราการรอดชีวิต, การตัดมดลูกออกแบบถอนรากถอนโคน*

Introduction

Cervical cancer is the fourth most common female cancers worldwide. In 2012, there were approximately 527,624 new cases of cervical cancer and 265,672 additional cases that resulted in death[1-3]. Moreover, it is the second most common cancer and the leading cause of death among women in Thailand[4]. Currently surgery is considered to be the gold standard treatment for early-stage cervical cancer patients, especially radical hysterectomy and pelvic lymphadenectomy (RHPL)[5,6]. The prognosis in early-stage cervical cancer is relatively reliable. A five-year survival rate of those patients is estimated to be 80-90%[7]. However, the survival rate after being treated with RHPL depends on several factors. Some studies have found that histology, tumor size, parametrial involvement, lymph vascular space invasion, pelvic lymph node metastasis, or even number of lymph node metastasis had a significant effect on the survival rate in early-stage cervical cancer patients[8-11]. Nevertheless, the assessment of independent prognostic factors that are helpful to predict survival and recurrence of disease is still needed.

The aim of this study was to evaluate prognostic factors and survival rates in early-stage cervical cancer patients who had been treated with RHPL.

Materials and Methods

A retrospective study was conducted at Department of Obstetrics and Gynecology, Buddhachinaraj Phitsanulok Hospital and approved by the Ethics Committee of Buddhachinaraj Phitsanulok Hospital. Seven hundred and thirty medical records of cervical cancer patients from January 1, 2005 to December 31, 2016 were retrospectively reviewed. The cervical cancer patients who had the International Federation of Gynecology and Obstetrics (FIGO) stage IA2-IIA and underwent RHPL reached the inclusion criteria for the study[12]. Twenty-one patients were excluded from the study due to incomplete medical records or limited data. Five of those patients had adenosquamous carcinoma subtype and 1 patient had neuroendocrine. Additionally, patients who received neoadjuvant chemotherapy were also excluded from the study. Thus, 177 patients who met the inclusion criteria were enrolled in this study (Fig. 1). The estimation of participants in this study was calculated by WG Cochran formula and the results of the study by Lee YY, et al[10], for the current study based on 95% confidence level and 80% power of test. The finite population correction for proportions formula was used to calculate the final cohort of participants, thus the adequate number of patients needed in this study was 230.

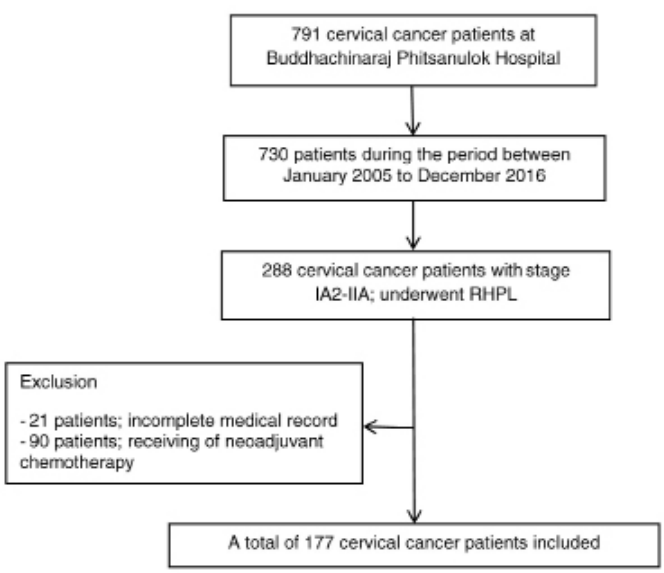

Fig. 1. Criteria Inclusion Flow Chart.

The clinical data including age, parity, body mass index (BMI), menstrual status, FIGO stage of cervical cancer, histology, presenting symptoms, tumor characteristics, surgical treatments, date of surgery, date of diagnosis of recurrence, and date of death from disease (if present) was collected. Tumor characteristics were classified as exophytic, infiltrative, ulcerative, and microscopic. Exophytic lesion was defined as a tumor that grew outward from an epithelial surface, while infiltrative lesion was the invasion of cancer cells into the underlying matrix of cervical tissue. Ulcerative lesion meant the carcinoma that invaded or destroyed cervical tissue causing indented lesion or ulcer. Patients who had any invisible lesions before undergoing RHPL were classified as microscopic. Surgical treatments were allocated as surgery alone, surgery followed by concurrent chemoradiotherapy (CCRT) or surgery followed by radiotherapy (RT).

The pathologic data consisted of surgical margins, parametrial involvement, pelvic lymph node metastasis, deep stromal invasion (DSI), lymph vascular space invasion (LVSI), and tumor size. DSI was defined as carcinoma invasion into the middle or deep third of total cervical stromal thickness, and LVSI as tumor invasion into the endothelium of vascular or lymphatic vessels. The measurement of tumor dimension was performed and reported by pathologists for accurate measurements, which were then divided into 2 groups: tumor size less than or equal to 4 centimeters (cm), and tumor size greater than 4 cm. The diagnosis of recurrence was confirmed with tissue biopsy or radio diagnostic tools such as chest x-ray, computerized tomography (CT) of the whole abdomen and/or a bone scan. Disease free survival (DFS) was defined as a period between initial operation and the recurrence of the disease. Meanwhile, cancer-specific survival (CSS) was declared as the time from initial operation to the time of death caused by cervical cancer; or for living patients, to the date of last follow up.

Statistical analysis was performed by using SPSS software version 22.0. The continuous data was demonstrated as mean and standard deviation (SD). For categorical variables, percentages were used. CSS and DFS curves were undertook the Kaplan-Meier method with log-rank test. The possible factors that could affect the recurrence of disease and survival rate including age, FIGO stage, treatments, histology, surgical margins, parametrial involvement, pelvic node metastasis, DSI, LVSI, and tumor size were analyzed in the univariate analysis, the multivariate analysis and the stratified survival analysis by using the Cox proportional hazards model. Any statistically significant data had a p value < 0.05.

Results

A total of 177 patients were enrolled in this study, mean age was 49.9 ± 11.0 years and mean BMI was 24.4 ± 4.1 kg/m^2. There were 5 patients in stage IA2, 157 patients in stage IB1-IB2, and 15 patients in stage IIA1-IIA2. Most patients 83.1% were in FIGO stage IA2-IB1 and the remaining 16.9% were in stage IB2-IIA (Table 1). There were only 2 histological subtypes identified, 125 patients were in the squamous cell carcinoma (SCC) group and 52 in the adenocarcinoma (AC) group. Other subtypes were not available due to limited data. The median follow-up time was 42 months (range 1-143 months). Twenty-five patients had a recurrence and 7 patients died from the disease. The five-year DFS rate and CSS rate were 89% and 96.6%, respectively. The pathologic findings were comprised of the surgical margins, parametrial involvement, pelvic lymph node metastasis, DSI, LVSI, and tumor size.

After using univariate analysis (Table 2), a prognostic factor that significantly impacted on DFS was increasing age (HR 1.05; 95%CI 1.01-1.08). Meanwhile, the significant prognostic factors for CSS were postoperative treatment with CCRT, and pelvic lymph node metastasis (HR 6.04; 95%CI 1.34-27.21, and HR 6.25; 95%CI 1.39-28.06, respectively).

Table 3 shows the multivariate analysis of DFS and CSS. The independent prognostic factors for DFS were increasing age and pelvic lymph node metastasis (HR, 1.06; 95% CI, 1.02-1.10, HR, 4.63; 95% CI, 1.21-17.64, respectively) whereas no significant results were found in the CSS.

Table 1. Clinicopathologic variables.

Characteristic	N = 177
Age (years), mean (SD)	49.9 (11.0)
Parity (%)	
0-1	39 (22.0)
2-3	121 (68.4)
≥ 4	17 (9.6)
BMI (kg/m^2), mean (SD)	24.4 (4.1)
Menstruation (%)	
Premenopuase	91 (51.4)
Postmenopause	86 (48.6)
FIGO stage (%)	
IA2-IB1	147 (83.1)
IB2-IIA	30 (16.9)
Histological subtypes (%)	
SCC	125 (70.6)
AC	52 (29.4)
Other subtypes	NA
Presenting symptoms (%)	
Check up	72 (40.7)
Vaginal bleeding	86 (48.6)
Pelvic pain	7 (3.9)
Abnormal discharge	12 (6.8)
Tumor characteristics (%)	
Exophytic	57 (32.2)
Infiltrative	37 (20.9)
Ulcerative	31 (17.5)
Microscopic	52 (29.4)
Treatment (%)	
Surgery alone	132 (74.6)
Surgery + CCRT	39 (22.0)
Surgery + RT	6 (3.4)
Positive surgical margin (%)	18 (10.2)
Parametrial involvement (%)	17 (9.6)
Pelvic lymph node metastasis (%)	35 (19.8)
Positive DSI (%)	118 (66.6)
Positive LVSI (%)	39 (22.0)
Tumor size (cm) (%)	
≤ 4	155 (87.6)
> 4	22 (12.4)

BMI, body mass index; FIGO, the International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; AC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; SD, standard deviation; DSI, deep stromal invasion; LVSI, lymph vascular space invasion; NA, not available.

Table 2. Univariate analysis for disease free survival and cancer-specific survival.

Variablesc	DFS		CSS	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.05 (1.01-1.08)	0.004*	0.94 (0.87-1.02)	0.161
FIGO stage				
IA2-IB1	1		1	
IB2-IIA	1.41 (0.56-3.35)	0.463	3.16 (0.70-14.22)	0.133
Treatment				
Surgery alone	1		1	
Surgery + CCRT	1.35 (0.54-3.40)	0.515	6.04 (1.34-27.21)	0.019*
Surgery + RT	NA	NA	NA	NA
Histological subtypes				
SCC	1		1	
Positive	1.68 (0.57-4.92)	0.337	1.41 (0.17-11.77)	0.747
AC	1.12 (0.48-2.60)	0.785	3.20 (0.71-14.31)	0.128
Surgical margin				
Negative	1		1	
Parametrial involvement				
Negative	1		1	
Positive	2.29 (0.78-6.69)	0.130	4.64 (0.89-24.07)	0.067
Pelvic lymph node metastasis				
Negative	1		1	
Positive	2.28 (0.98-5.28)	0.055	6.25 (1.39-28.06)	0.017*
Deep stromal invasion				
Negative	1		1	
Positive	1.05 (0.46-2.38)	0.907	0.78 (0.17-3.51)	0.753
Lymph vascular space invasion				
Negative	1		1	
Positive	0.70 (0.24-2.04)	0.518	2.77 (0.62-12.37)	0.182
Tumor size (cm)				
≤ 4	1		1	
> 4	1.33 (0.39-4.45)	0.645	4.00 (0.76-20.95)	0.101

DFS, disease free survival; CSS, cancer-specific survival; FIGO, the International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; AC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval; NA, not available.
*Significance at $p < 0.05$

Table 3. Multivariate analysis for disease free survival and cancer-specific survival.

Variables	DFS		CSS	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.06 (1.02-1.10)	0.004*	0.94 (0.86-1.03)	0.230
FIGO stage				
IA2-IB1	1		1	
IB2-IIA	1.89 (0.66-5.38)	0.230	0.96 (0.10-8.47)	0.971
Treatment				
Surgery alone	1		1	
Surgery + CCRT	0.19 (0.02-1.42)	0.106	5.46 (0.14-20.72)	0.355
Surgery + RT	NA	NA	NA	NA
Histological subtypes				
SCC	1		1	
AC	1.33 (0.53-3.31)	0.533	5.21 (0.77-35.07)	0.089
Surgical margin				
Negative	1		1	
Positive	2.05 (0.34-12.23)	0.430	0.71 (0.02-21.43)	0.847
Parametrial involvement				
Negative	1		1	
Positive	1.38 (0.23-8.07)	0.715	6.37 (0.32-12.75)	0.225
Pelvic lymph node metastasis				
Negative	1		1	
Positive	4.63 (1.21-17.64)	0.025*	2.11 (0.16-26.92)	0.563
Deep stromal invasion				
Negative	1		1	
Positive	1.06 (0.41-2.70)	0.895	0.31 (0.02-3.65)	0.356
Lymph vascular space invasion				
Negative	1		1	
Positive	0.79 (0.24-2.63)	0.709	1.66 (0.19-13.95)	0.640
Tumor size (cm)				
≤ 4	1		1	
> 4	1.06 (0.18-5.97)	0.945	0.55 (0.03-9.08)	0.683

DFS, disease free survival; CSS, cancer-specific survival; FIGO, the International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; AC, adenocarcinoma; HR, hazard ratio; CI, confidence interval; NA, not available. *Significance at $p < 0.05$

Fig. 2 demonstrates the correlation between DFS and pelvic lymph node metastasis. There were no significant differences in FIGO stage, histology, positive surgical margin, parametrial involvement, pelvic lymph node metastasis, DSI, LVSI, or tumor size that were identified as independent prognostic factors for CSS. However, the stratified survival analysis calculated the survival outcome between SCC and AC (Table 4), where AC patients with parametrial involvement, pelvic lymph node metastasis, or postoperative treatment followed by CCRT had a significantly worse survival outcome than those with SCC (HR, 11.87; 95% CI, 1.46-46.20, HR, 7.00; 95% CI, 1.55-31.66, HR, 7.20; 95% CI, 1.57-32.85, respectively).

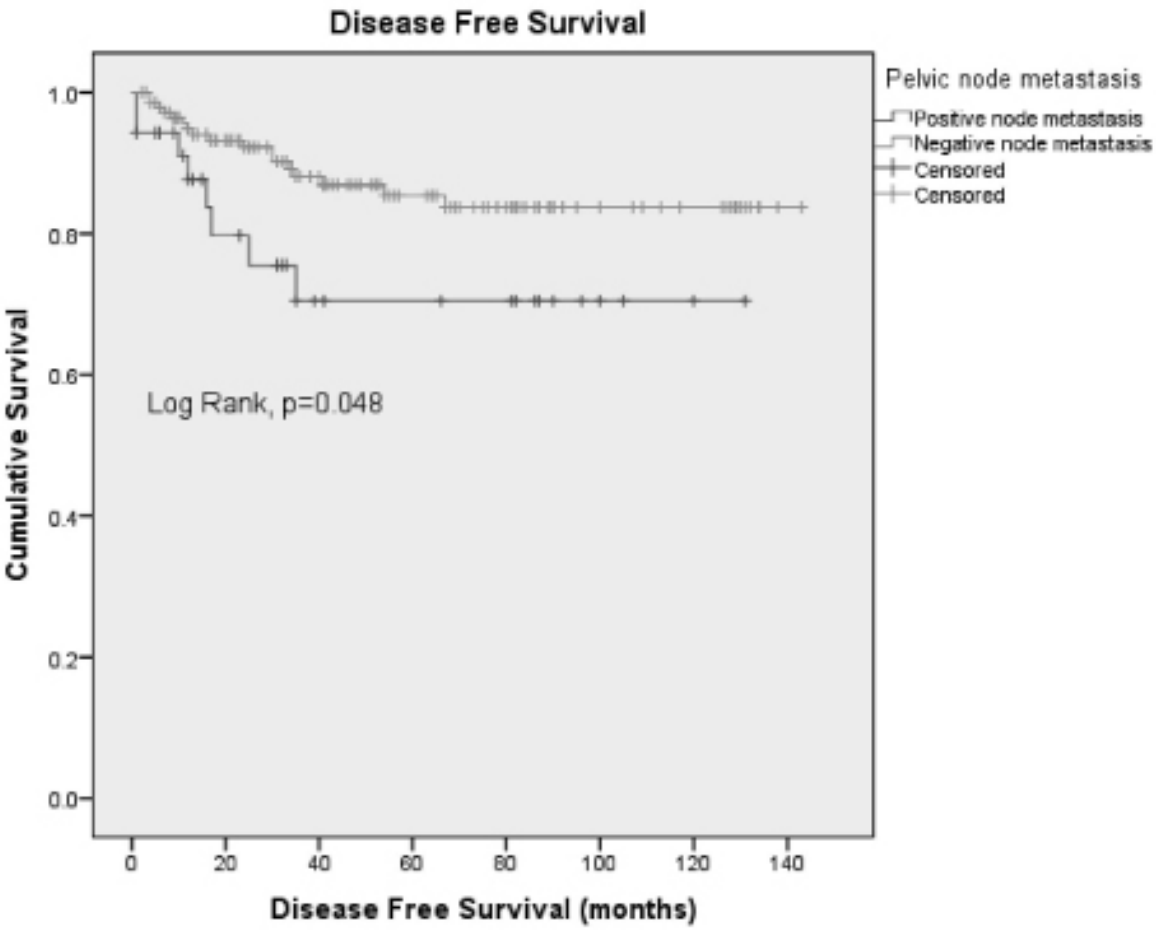

Fig. 2. Disease free survival based on pelvic node metastasis after radical hysterectomy and pelvic lymphadenectomy.

Table 4. Stratified survival analysis for cancer-specific survival.

Variables	SCC (n = 125)		AC (n = 52)		HR (95% CI)	p value
	n	Event (%)	n	Event (%)		
Overall	125	3 (2.4)	52	4 (7.6)		
Age	125	3 (2.4)	52	4 (7.6)	0.94 (0.87-1.02)	0.179
FIGO stage						
IA2-IB1	104	1 (1.0)	43	3 (6.9)	1	
IB2-IIA	21	2 (9.5)	9	1 (11.1)	3.38 (0.75-15.21)	0.112
Treatment						
Surgery alone	88	1 (1.1)	44	2 (4.5)	1	
Surgery + CCRT	31	2 (6.4)	8	2 (25.0)	7.20 (1.57-32.85)	0.011*
Surgery + RT	6	0 (0.0)	0	0 (0.0)	NA	NA
Surgical margin						
Negative	109	3 (2.7)	50	3 (6.0)	1	
Positive	16	0 (0.0)	2	1 (50.0)	2.10 (0.23-18.81)	0.506
Parametrial involvement						
Negative	109	2 (1.8)	51	3 (5.8)	1	
Positive	16	1 (6.2)	1	1 (100.0)	11.87 (1.46-46.20)	0.020*
Pelvic node metastasis						
Negative	97	1 (1.0)	45	3 (6.6)	1	
Positive	28	2 (7.1)	7	1 (14.3)	7.00 (1.55-31.66)	0.011*
Deep stromal invasion						
Negative	37	1 (2.7)	22	2 (9.1)	1	
Positive	88	2 (2.3)	30	2 (6.6)	1.09 (0.22-5.25)	0.910
LVSI						
Negative	93	2 (2.1)	45	2 (4.4)	1	
Positive	32	1 (3.1)	7	2 (28.6)	3.65 (0.78-16.88)	0.098
Tumor size (cm)						
≤ 4	107	1 (1.0)	48	4 (8.3)	1	
> 4	18	2 (11.1)	4	0 (0.0)	4.59 (0.86-24.31)	0.073

FIGO, the International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; AC, adenocarcinoma; LVSI, lymph vascular space invasion; HR, hazard ratio; CI, confidence interval; NA, not available.
*Significance at $p < 0.05$

Discussion

According to the most recent statistical data for survival rates, there has been a good survival rate in early-stage cervical cancer. Similar results were found in this study; a 5-year DFS rate and a 5-year CSS rate of 89% and 96.6% respectively. Likewise, other studies revealed the 5-year survival rates in patients who underwent RHPL were more than 90%[13,14]. One research was conducted on surgical outcomes and prognostic factors in early-stage cervical cancer during

the past 12 years; its 5-year DFS rate was 84%, which concurred with the result found in this study[15].

From the univariate analysis, increasing age was found to be the only significant factor that impacted DFS. It showed that an increasing age every 1 year significantly increased the risk of recurrence for 1.05 times. One study discovered that age was a significant prognostic factor for both DFS and CSS[16]. However, after adjusting confounding values by using the multivariate analysis, increasing age and pelvic node metastasis were independent prognostic factors in this study. Likewise, some studies supported that pelvic node metastasis was independent prognostic factor for DFS[15,17,18].

In the previous studies, there have been many significant prognostic factors that affected the CSS such as tumor stage, tumor size larger than 4 cm, pelvic node metastasis, number of positive pelvic node, and histological subtype[11,17,19,20]. Compared to this study, postoperative treatment followed by CCRT and pelvic node metastasis were the significant factors that correlated to CSS after using the univariate analysis. The patients whose pathological findings had a positive surgical margin, parametrial involvement, or pelvic lymph node metastasis required treatment with CCRT as the Hospital's protocol. It was found that patients in the postoperative treatment followed by CCRT group had a significantly poorer survival rate, by 6 times, compared to that of the patients who underwent surgery alone. Data was unable to be interpreted for the postoperative treatment followed by RT group due to the small number of patients.

With regards to the National Comprehensive Cancer Network guidelines[21], if the cervical cancer patients had a negative LVSI, a positive 1/3 middle or deep stromal invasion, and a tumor size equal to or greater than 4 cm; an adjuvant pelvic radiation was also necessary. Sixty-six percent of the participants in this study had DSI, but mostly negative LVSI in any tumor sizes which did not meet the criteria for pelvic radiation after RHPL, possibly leading to a lower number of patients in the RT group. Nevertheless, no statistically significant prognostic factors for CSS were found in the multivariate analysis. The reason for varying results from previous studies may be reflected by the variance of patient demographic data, number of participants, type of treatment and follow-up time.

Despite no independent prognostic factors for CSS were found, the secondary outcome in this study after using the stratified survival analysis showed that the patients with the histology of AC had a significantly worse survival rate than those with SCC if there was parametrial involvement, pelvic node metastasis, and postoperative treatment followed by CCRT. Several studies supported that AC was one of the independent prognostic factors that impacted CSS[10,22]. In contrast, histology did not have any influences on CSS in some studies, comparable to the findings[13,23,24]. Few studies discussed the prognostic factors in AC patients who had been treated with RHPL, and the results showed that pelvic lymph node metastasis or parametrial involvement were significant prognostic factors to predict survival outcome in AC[23,25].

The strengths of this study were the collection of data that originated from a single institution that was able to treat patients with cervical cancer. Moreover, all of pathologic findings were performed and reported by experienced pathologists at the Hospital, providing precise measurements. However, the study design was retrospective and involved a long period of data collection as a result, bias could have occurred and results were interpreted cautiously. The consequence from a long period of data was that some important information had not been available at the time of collection. Other limitations were the inadequate number of patients and the low number of participants for postoperative treatment followed by RT, where the statistical analysis was unable to draw a conclusive result, which may have affected the result of survival rates. A future study may involve one with a prospective design and larger number of patients.

Conclusion

Early-stage cervical cancer patients who had been treated with RHPL showed good survival rates. The independent prognostic factors for DFS were

increasing age and pelvic lymph node metastasis. In contrast, no independent prognostic factors for CSS were identified after using the multivariate analysis. It was found that parametrial involvement, pelvic lymph node metastasis, and postoperative treatment followed by CCRT were likely to be predictors for a worse survival outcome in AC than in SCC. Furthermore, this study may be a useful database with reference to cervical cancer at the Hospital, and/or used for counseling cervical cancer patients in relations to prognosis and further management.

Potential conflicts of interest

The authors declare no conflict of interest.

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RETRACTION

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